Patient-specific cardiovascular modeling in pulmonary hypertension : assessment of hemodynamic and mechanical ventricular interaction

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Patient-Specific Cardiovascular Modeling in Pulmonary Hypertension

Assessment of Hemodynamic and
Mechanical Ventricular Interaction

Joost Lumens

Patient-Specific Cardiovascular Modeling in Pulmonary Hypertension

Assessment of Hemodynamic and Mechanical Ventricular Interaction

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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als ik die dikke boeken zie van de geleerden
vol wijze dingen die zij allemaal beweerden
en ik zie de wereld om me heen, dan moet ik vrezen
dat niemand ooit die wijze boeken heeft gelezen

Toon Hermans

Colofon

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Chapter 1

General Introduction

GENERAL INTRODUCTION

Pulmonary hypertension (PH) is a pathological condition that is characterized by elevated blood pressure in the pulmonary artery. PH has been defined clinically as a mean pulmonary artery pressure, measured by right heart catheterization, of >25 mmHg at rest, or >30 mmHg with exercise.¹ The most recent clinical classification of PH (Dana Point classification) distinguishes five subgroups.³⁹ Each subgroup of PH shares pathological and clinical features as well as similar therapeutic options. In this thesis, we focus on two subgroups, i.e., pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). PAH is defined as a group of diseases with a common characteristic histopathological pattern of pulmonary vascular remodeling. This vascular remodeling results in resistive lesions in the pulmonary vascular bed progressively leading to chronic elevation of pulmonary arterial pressure.^{16, 38} PAH is a rare disease as evidenced by low estimates of prevalence and incidence, i.e., 15.0 cases per million of adult inhabitants and 2.4 cases per million of adult inhabitants per year, respectively.²² Furthermore, CTEPH is a late-occurring complication of pulmonary embolism.^{3, 34} CTEPH can be considered as a type of PAH, since it also progressively develops due to similar histopathological changes in the pulmonary vasculature as seen in other forms of severe nonthromboembolic PAH.^{11, 15, 32} In the remainder of this thesis, the term PAH also includes CTEPH, unless stated differently.

When left untreated, PAH progressively leads to right heart failure and premature death within 2.8 years from diagnosis.^{9, 29, 38} Several studies showed that morbidity and mortality of PAH patients are determined by the ability of the right ventricle (RV) to maintain normal stroke volume and cardiac output despite pressure overload.^{8, 31, 32, 35, 36}

Historically, knowledge of RV pump function under normal as well as under pathological conditions has lagged behind that of the left ventricle (LV).¹⁷ Consequently, the mechanisms of RV failure are poorly understood. Over the last decade, however, the RV is gaining interest, partly driven by the insight that RV performance is of pivotal importance in patients with PAH.^{8, 17, 19, 20, 28, 41} The LV and the RV are functionally dependent due to their mechanical interaction via the interventricular septum and their hemodynamic series interaction via the pulmonary and systemic circulations.^{2, 4-6, 10, 13, 14, 23, 25, 33, 37, 40, 42} Thus, in daily clinical practice, understanding the mechanisms of ventricular interaction is also essential for proper treatment of right heart failure in PAH.

GENERAL AIM OF THE THESIS

In this thesis, we aim to elucidate the mechanisms by which PAH affects left and right ventricular pump function. For that purpose, we developed a mathematical model of cardiovascular mechanics incorporating hemodynamic and mechanical ventricular interaction. This model was used for hypothesis-driven investigation of the effect of PAH on cardiac pump function. Each of these investigations starts with fitting the model to the average of a set of clinical measurements obtained in patients with PAH in order to obtain a representative pathology-specific simulation of ventricular mechanics and hemodynamics as function of time. Using the pathology-specific simulation as point of departure, the model was used 1) to test pacing of the RV free wall for its potential to treat RV failure in patients with severe PAH, 2) to quantify contributions of mechanical and hemodynamic ventricular interaction to LV filling hemodynamics in patients with CTEPH before and after surgically induced decrease of pulmonary vascular resistance, and 3) to assess ventricular mechanics patient-specifically for better understanding of ventricular mechanical asynchrony in the individual PAH patient.

OUTLINE OF THE THESIS

The thesis starts with an introduction to relevant aspects of cardiac anatomy and physiology in **chapter 2**. The influence of PAH on cardiac anatomy and physiology is also addressed in this chapter.

Chapters 3 and 4 comprise the mathematical basis of a new three-wall segment model (TriSeg model) describing ventricular mechanics and hemodynamics incorporating mechanical interaction of the LV free wall, the interventricular septum, and the RV free wall.

In **chapter 3**, the TriSeg model is introduced and used to simulate ventricular mechanics and hemodynamics with normal synchronous and with abnormal asynchronous mechanical activation of the ventricular walls. Simulation results of ventricular geometries and pressures are compared with experimental data obtained in dogs before and after acute induction of left bundle branch block, i.e., delayed onset of mechanical activation of the LV free wall compared to that of the interventricular septum and RV free wall.

The theory of the TriSeg model is described elaborately in **chapter 4**. The model is used to simulate cardiac mechanics and hemodynamics with normal

mechanical loading, with acute increase of pulmonary vascular resistance, and with increase of pulmonary vascular resistance including adaptation of the ventricular walls to increased mechanical load. Simulation results are compared with clinical data on ventricular mechanics and hemodynamics as obtained in healthy volunteers and in patients with PAH. Furthermore, the relation between geometry of the interventricular septum and its transmural pressure difference, as simulated, is compared with this relation as measured in patients with and without PAH.

In the second part of the thesis (**chapters 5-7**), the model is used to obtain a better understanding of the cardiac pathophysiology in PAH and to quantify the effect of therapeutic interventions on cardiac pump function.

In PAH, duration of myofiber shortening is prolonged in the RV free wall as compared to that in the interventricular septum and LV free wall.²⁷ This ventricular mechanical asynchrony eventually leads to right heart failure. It has also been shown that PAH is associated with electrophysiological changes in the RV free wall, i.e., conduction slowing and action potential prolongation.^{7, 21, 24} We used the model to explore whether early pacing of the RV free wall may improve interventricular mechanical synchrony and, hence, cardiac pump function in patients with severe PAH (**chapter 5**).

In patients with CTEPH, chronic increase of RV afterload is associated with an abnormal LV filling pattern,^{12, 18, 26, 30} i.e., early diastolic peak of mitral blood flow velocity (E) is smaller than the peak flow velocity related to atrial contraction (A). Pulmonary thromboendarterectomy is a surgical intervention that acutely reduces pulmonary vascular resistance and is associated with acute increase of mitral E/A-ratio.^{18, 26, 30} Resolution of leftward septal bulging and increase in RV systolic output are thought to be responsible for the increase of the E/A-ratio. The TriSeg model is used to quantify the separate contributions of leftward septal bulging and of RV systolic output to LV filling hemodynamics in a group of CTEPH patients before and after pulmonary thromboendarterectomy (**chapter 6**).

A patient specific simulation approach is designed to assess the mechanism of ventricular mechanical asynchrony in the individual patient with PAH (**chapter 7**).

The thesis ends with **chapter 8**, a general discussion linking the findings of abovementioned studies and putting them in a broader perspective. Potential clinical implications are discussed and are followed by suggestions for related future studies.

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Chapter 2

**Cardiac Anatomy and Physiology
Under Normal and Pulmonary
Hypertensive Conditions**

THE HEART AS A PUMP

The heart is a dual pump that drives the blood in two serial circuits, i.e., the pulmonary and the systemic circulation (*Figure 2.1*). The pump work needed to achieve blood circulation is delivered by four hollow chambers enclosed by muscular walls (*Figure 2.2*). Deoxygenated blood returning from the systemic circulation arrives via the coronary sinus and the inferior and superior vena cava in the right atrium. Via the tricuspid valve, the blood then enters the right ventricle (RV). The RV pumps the blood via the pulmonary valve through the main pulmonary artery into the pulmonary peripheral circulation. The pulmonary circulation then provides the blood with oxygen and removes carbon dioxide. Subsequently, the oxygenated blood returns to the heart and arrives in the left atrium via the pulmonary veins. Via the mitral valve, the blood enters the left ventricle (LV). The LV propels the blood via the aortic valve through the aorta into the systemic peripheral circulation, i.e., body organs and tissues. Finally, the blood re-enters the right atrium via the coronary sinus and the venae cavae, thus closing the circulation.

Figure 2.1 Schematic representation of the human cardiovascular system. The pulmonary and the systemic circulation are coupled in series with the heart in between them. The right heart receives deoxygenated blood from the body tissues and pumps it into the pulmonary circulation. After passing the lungs, the oxygenated blood enters the left heart which pumps the blood into the systemic circulation to supply the body tissues. [Adapted from E.N. Marieb, *Human Anatomy and Physiology*. Fourth Edition. Benjamin Cummings, 1998]

Figure 2.2 Anatomy of the heart. This schematic representation shows a cross-section of the heart along its long axis. Abbreviations: LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. [Adapted from E.N. Marieb, *Human Anatomy and Physiology*. Fourth Edition. Benjamin Cummings, 1998]

STRUCTURE AND FUNCTION OF THE CARDIAC WALLS

The myocardial walls of the heart mainly consist of two types of cells, i.e., myocytes and fibroblasts.^{17, 33, 34} Myocytes are responsible for contraction of the heart. Inside the myocytes, contractile force is generated by contractile units called sarcomeres. Locally, myocytes are more or less aligned to form myofibers.^{24, 61} Myocytes are embedded in the extra-cellular matrix, a fibrous network mainly consisting of collagen. The extra-cellular matrix plays an important role in transmitting the contractile force generated by the sarcomeres to the ventricular chamber. Fibroblasts play a pivotal role in the regulation of composition and structure of the extra-cellular matrix.⁶⁰

THE CARDIAC CYCLE

Figure 2.3 shows the time courses of atrial, ventricular, and arterial pressures as well as ventricular volumes and flows through valves during a cardiac cycle of the normal human heart. A cardiac pump cycle is generally divided into the phases of filling, isovolumic contraction, ejection, and isovolumic relaxation. As shown by the time courses of blood flow through the mitral and tricuspid valves (*Figure 2.3*), the filling phase can be divided in an early diastolic filling phase (E-wave) and a subsequent active filling phase induced by atrial contraction (A-wave). In *Figure 2.3*, the cardiac cycle starts with atrial contraction and thus with the A-wave of ventricular filling and the related increase of ventricular pressure. Next, the myofibers in the ventricular walls are activated. Increase of ventricular pressure beyond atrial pressure causes closure of the atrioventricular valve (mitral or tricuspid valve). During the subsequent isovolumic contraction phase, further mechanical activation of the myofibers in the ventricular walls causes additional increase of ventricular pressure while ventricular volume remains constant with all valves closed. Increase of ventricular pressure beyond arterial pressure causes opening of the ventriculoarterial valve (aortic or pulmonary valve). Subsequently, blood is ejected into the large arteries (aorta and pulmonary artery). At the end of ejection, the myofibers relax and ventricular pressure drops below arterial pressure, causing closure of the ventriculoarterial valve. During the subsequent isovolumic relaxation phase, ventricular pressure drops further while ventricular volume remains constant since all valves are closed. Decrease of ventricular pressure below atrial pressure causes opening of the atrioventricular valve and results in an early diastolic filling wave (E-wave). During the latter passive filling phase, ventricular cavity volume increases rapidly and atrial and ventricular pressures evolve in parallel.

As depicted in *Figure 2.3*, the shapes of the pressure tracings of the left and right heart are quite similar. However, pressures in the right heart (*Figure 2.3A*) are about one fifth of those in the left heart (*Figure 2.3B*). Under hemodynamic steady-state conditions, volume changes of the LV are the same as those of the RV because both ventricles eject the same amount of blood. Despite small left-to-right differences in timing of valve opening and closure, hemodynamic tracings show relative left-right synchrony of contractions and associated hemodynamics.

Figure 2.3 Time courses of blood pressures, ventricular volumes, and blood flows through cardiac valves during a cardiac cycle of a normal adult at rest. **A:** right heart hemodynamics. **B:** left heart hemodynamics. Note that the cardiac cycle is divided into four phases separated by moments of cardiac valve opening and closure, i.e., ventricular filling, isovolumic contraction (IC), ventricular ejection, and isovolumic relaxation (IR). Note that the filling phase is subdivided into an early passive filling wave (E) and a late active filling wave (A) induced by atrial contraction. Abbreviations: LA = left atrial; LV = left ventricular; RA = right atrial; RV = right ventricular.

Assessment of Global Ventricular Pump Load and Local Myofiber load

During the cardiac cycle, a loop is formed by ventricular cavity pressure as function of cavity volume (*Figure 2.4A*). This pressure-volume loop represents the global mechanical pump load of the ventricle during a single cardiac cycle. The area of the pressure-volume loop quantifies external mechanical stroke work as generated by the ventricle. As depicted for the LV in *Figure 2.4A*, the ventricular pressure-volume loop is bounded by two curves quantifying the passive and active mechanical behavior of the ventricle as a chamber.

Figure 2.4 Assessment of ventricular mechanical load during a cardiac cycle of a normal adult at rest. **A:** global mechanical left (LV) and right (RV) ventricular pump load as expressed by cavity pressure-volume loops. The shaded area of the pressure-volume loop represents ventricular stroke work. **B:** local mechanical tissue load as expressed by a myofiber Cauchy stress-natural strain loop. The shaded area of the myofiber stress-strain loop represents myofiber stroke work density. Ventricular pressure-volume loops and myofiber stress-strain loops are bounded by two curves describing the passive and active behavior of the myocardium. Moments of aortic/pulmonary valve opening ($\circ$) and closure ($\bullet$) and of mitral/tricuspid valve opening ($\square$) and closure ($\blacksquare$) are indicated and divide the cardiac cycle in four phases, i.e., ventricular filling, isovolumic contraction (IC), ventricular ejection, and isovolumic relaxation (IR).

At local tissue level, a loop is formed by myofiber stress as function of myofiber strain during a cardiac cycle (*Figure 2.4B*). This myofiber stress-strain loop represents local mechanical load of the myofiber during a single cardiac

cycle. In this thesis, myofiber stress is defined as Cauchy stress, i.e., the force per unit of cross-sectional area of the myofiber in the actual state. Myofiber strain is defined as natural strain, i.e., natural logarithm of the ratio of myofiber length to an arbitrary reference length. The area of the myofiber stress-strain loop quantifies mechanical stroke work density, i.e., contractile myofiber stroke work per unit of tissue volume. Analogous to the ventricular pressure-volume loop, the myofiber stress-strain loop is bounded by two curves quantifying the passive and active mechanical behavior of the local myocardial tissue (*Figure 2.4B*). Myofiber stress in passively stressed myocardial tissue increases about exponentially with myofiber strain.^{15, 30} At low sarcomere length, myocardial tissue stiffness is mainly determined by components of the myocyte cytoskeleton such as titin.^{23, 73} At larger sarcomere length, collagen in the extra-cellular matrix becomes stretched and, thereby, increases myocardial tissue stiffness and prevents myocardial overstretch during filling. Furthermore, passive mechanical behavior of the myocardial tissue is anisotropic, i.e., along the myofiber axis, the tissue is significantly stiffer than in the direction perpendicular to the myofiber axis. In the actively contracting state, myocardial tissue shows a more linear relation between myofiber stress and strain. Local force actively generated by the myofibers depends, among other parameters, on time after activation, sarcomere length, sarcomere shortening velocity,^{12, 26, 36, 64} as well as on the mechanical boundary conditions imposed by the surrounding tissue.

Under normal cardiac loading conditions at rest, the RV ejects the blood against relatively low arterial pressure (mean pulmonary artery pressure ≈ 15 mmHg) as compared to the LV (mean aortic pressure ≈ 90 mmHg). Consequently, mechanical pump stroke work of the RV is about six times lower than that of the LV when assuming equal stroke volume. This difference in ventricular pump load is associated with differences in gross anatomy of both ventricles. The RV free wall is relatively thin compared to the LV free wall and the interventricular septum, the latter two having quite similar wall thicknesses (*Figure 2.5*, upper row).²⁹ Furthermore, non-invasively obtained imaging data revealed that, in healthy subjects, the LV free wall accounts for about half of the total ventricular wall mass of about 200 g,⁴¹ whereas the RV free wall and the interventricular septum both account for about a quarter.

The pump work generated by the LV and the RV is the resultant of the summed action of all individual myocytes in the ventricular walls. Myofiber stress, force, and cavity pressure are closely related quantities. Similarly, myofiber strain is closely related to changes in sarcomere length and cavity volume. The quantitative relation between global ventricular pump function, as expressed in

terms of cavity pressure and volume, and local contractile tissue function, as expressed in terms of myofiber stress and strain, is not straightforward. Since it is hard to measure myofiber stress *in vivo*,^{19, 44} researchers have used mathematical models to assess this relation. Most of these models are based on finite element analysis.^{8, 9, 37, 52, 66, 68} Finite element models allow description of local wall mechanics and geometry and can, thus, deal with regional non-uniformities in the myocardial walls, e.g., asynchrony of activation or reduced contractile performance in case of myocardial infarction. Finite element models of the heart are computationally demanding due to their complexity. In an attempt to simplify the relation between myocardial tissue mechanics and pump function in the normal heart, Arts *et al.*¹ found that the ratio of ventricular cavity to wall volume was the most important determinant for average myofiber stress and strain in the wall, while actual geometry appeared of minor importance. This finding was incorporated in the relatively simple one-fiber model relating ventricular cavity pressure and volume to myofiber stress and strain. The one-fiber model was based on the assumption that, in the normal heart, myofiber structure and geometry adapt until myofiber load is evenly distributed over the myocardial wall.³ For study of beat-to-beat hemodynamics and mechanics of the heart and the blood vessels, the one-fiber concept has been used to develop the lumped closed-loop CircAdapt model of heart and circulation.² The CircAdapt model consists of a network of modules representing myocardial walls, valves, large blood vessels, and peripheral resistances. It allows beat-to-beat simulation of time-dependent cardiovascular mechanics and hemodynamics, e.g., cavity volumes and pressures of the cardiac chambers, pressures in the large blood vessels, myofiber stress and strain in the cardiac walls, and flows through valves. An important feature of the CircAdapt model is that the number of independent parameters is reduced by incorporating adaptation of cardiac and vascular wall size and wall mass to mechanical load so that stresses and strains in the walls of heart and blood vessels are normalized to tissue-specific physiological standard levels.^{2, 43}

Figure 2.5 Midventricular short axis magnetic resonance images as obtained in a normal healthy adult (NORMAL) and in a patient with severe pulmonary arterial hypertension (PAH). In the normal heart, the septum (Sept) is concave toward the left ventricular (LV) cavity during the entire cardiac cycle. In the PAH heart, the Sept is concave toward the right ventricular (RV) cavity and shows most leftward bulging during early LV filling. Note the hypertrophic RV free wall (RVfw), the dilated RV cavity, and the small LV cavity in the PAH heart. Thickness of the LV free wall (LVfw) and of the septum are similar in the normal heart as well as in the PAH heart. The magnetic resonance images are used by courtesy of Marcus *et al.*⁴⁷

Ventricular Interaction

Ventricular interaction refers to the concept of mutual mechanical and hemodynamic dependence of the LV and the RV. Three anatomic aspects of the cardiovascular system are responsible for ventricular interaction. First, hemodynamic interaction between the RV and the LV is achieved by their series coupling via the pulmonary circulation and the systemic circulation. In a normal heart under hemodynamically steady-state conditions, each ventricle ejects all the blood that it receives from the other ventricle. Second, the direct anatomical coupling of the ventricles results in a strong mechanical interaction via the interventricular septum. A change of shape, size, or pressure-volume relation of one ventricle affects shape, size, and pressure-volume relation of the other ventricle through the septum.^{4, 16, 54, 58, 72} This phenomenon has been elegantly demonstrated with experiments in cardiac preparations in which direct mechanical ventricular interaction via the septum had been preserved but series

ventricular interaction via the pulmonary circulation had been abolished.^{18, 51, 63, 69} These studies showed that increase of RV pressure, while keeping LV pressure and filling volume artificially constant, increased LV end diastolic pressure as a direct result of geometrical changes such as leftward septal bulging. Third, the relatively stiff pericardial sac surrounding the heart limits acute cardiac distension and, thereby, modulates mechanical ventricular interaction. Experimental studies in animals and in patients have shown that pericardial constraint has little but significant effect on diastolic ventricular mechanics and negligible effect on systolic mechanics under normal physiological circumstances at rest.^{31, 46} However, pericardial constraint has a significant effect on diastolic and systolic ventricular mechanics and hemodynamics with acute pulmonary hypertension or RV volume overload.^{5, 6} Other studies showed that the pericardium is capable of adapting over time to changes in cardiac size and geometry.^{7, 20}

Effect of Pulmonary Arterial Hypertension on Ventricular Pump Function and Anatomy

With pulmonary arterial hypertension (PAH), progressive remodeling and vasoconstriction of the pulmonary vasculature leads to gradual increase of pulmonary vascular resistance. To maintain cardiac output, RV pressure is increased and may finally approach or even exceed LV pressure. In early stages of disease, the heart manages to compensate for the increase of RV afterload by increasing RV free wall mass (hypertrophy) so that wall stress is decreased to normal physiological value.^{11, 25} In animal models of PAH,^{50, 53} the early hypertrophic response comprises significant increase of diameter and number of myocytes in the RV free wall, whereas myocyte length and average sarcomere length remained unchanged. With further aggravation of PAH, however, RV contractile function deteriorates and RV end-diastolic volume increases.^{28, 59} Subsequently, wall tension and myocardial oxygen demand increase in the RV free wall, while coronary perfusion is locally diminished.⁶⁷ Finally, these morphological and functional changes lead to decompensated right heart failure characterized by rise of RV filling pressures, development of RV diastolic dysfunction, RV dilatation, and decrease of cardiac output.⁷⁰ Several RV diastolic function parameters correlate well with mean pulmonary artery pressure and with prognostic parameters assessing the risk of heart failure in patients with PAH.^{21, 74}

In severe PAH, RV dilatation is usually associated with functional tricuspid regurgitation due to dilatation of the tricuspid annulus followed by inability of

the tricuspid leaflets to coapt properly. The resultant increase of RV volume overload accelerates the transition from compensation to decompensated right heart failure. Significant reduction of RV afterload by surgical treatment has been shown to diminish tricuspid regurgitation in patients with PAH.^{10, 57, 65}

In PAH, the most distinct characteristic is the abnormal geometry and motion of the interventricular septum.^{32, 56, 62} Several studies showed that septal geometry and motion are of diagnostic and predictive significance in patients with PAH.^{35, 38} As mentioned previously, curvature of the septum is directly related to its transmural pressure gradient.^{13, 16, 39, 40, 55} As depicted in the upper row of *Figure 2.5*, the septum of the normal heart is concave toward the LV cavity during the entire cardiac cycle. However, with increase of RV pressure due to PAH, the septum flattens and may even bulge toward the LV cavity (*Figure 2.5*, lower row). In severe PAH, the septum often experiences a rapid leftward motion during the LV isovolumic relaxation phase and during early LV filling. During this period, pressure in the RV shortly exceeds that in the LV due to delayed RV pressure decay.⁶² Furthermore, shortening of the RV free wall is prolonged compared to that of the LV free wall and the septum.^{47, 71} Although the latter left-right delay of shortening correlates with an estimate of wall tension in the RV free wall,⁴⁷ the precise reason for this interventricular mechanical and hemodynamic asynchrony is still unknown. In **Chapter 5** and **Chapter 7**, a computer model is used to investigate the mechanism of interventricular mechanical and hemodynamic asynchrony in PAH. Furthermore, it is tested whether early pacing of the RV free wall may improve interventricular mechanical synchrony and, hence, cardiac pump function in patients with severe PAH (**Chapter 5**).

In patients with PAH, chronic increase of pulmonary vascular resistance is associated with reduced LV end-diastolic volume and abnormal LV filling pattern,^{14, 22, 27, 42, 45, 48, 49, 71} i.e., early diastolic peak of mitral blood flow velocity appears smaller than the peak of mitral flow velocity related to left atrial contraction. This phenomenon might be due to leftward septal bulging, which is believed to hinder passive filling by compressing the LV. Alternatively, the inability of the RV to maintain normal stroke volume is believed to reduce preload of the LV. Although Gurudevan *et al.*²⁷ suggested that the latter mechanism is the dominant disturbing factor in patients with chronic thromboembolic pulmonary hypertension, it is still unclear to what extent both mechanisms contribute to the change of LV filling hemodynamics in these patients. In **Chapter 6**, the separate contributions of both mechanisms are quantified in patients with chronic thromboembolic pulmonary hypertension to obtain better understanding of the mechanism by which PAH affects LV filling.

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Chapter 3

Modeling Ventricular Interaction:

a Multiscale Approach from Sarcomere Mechanics
to Cardiovascular System Hemodynamics

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ABSTRACT

Direct ventricular interaction via the interventricular septum plays an important role in ventricular hemodynamics and mechanics. A large amount of experimental data demonstrates that left and right ventricular pump mechanics influence each other and that septal geometry and motion depend on transmural pressure. We present a lumped model of ventricular mechanics consisting of three wall segments that are coupled on the basis of balance laws stating mechanical equilibrium at the intersection of the three walls. The input consists of left and right ventricular volumes and an estimate of septal wall geometry. Wall segment geometry is expressed as area and curvature and is related to sarcomere extension. With constitutive equations of the sarcomere, myofiber stress is calculated. The force exerted by each wall segment on the intersection, as a result of wall tension, is derived from myofiber stress. Finally, septal geometry and ventricular pressures are solved by achieving balance of forces. We implemented this ventricular module in a lumped model of the closed-loop cardiovascular system (CircAdapt model). The resulting multiscale model enables dynamic simulation of myofiber mechanics, ventricular cavity mechanics, and cardiovascular system hemodynamics. The model was tested by performing simulations with synchronous and asynchronous mechanical activation of the wall segments. The simulated results of ventricular mechanics and hemodynamics were compared with experimental data obtained before and after acute induction of left bundle branch block in dogs. The changes in simulated ventricular mechanics and septal motion as a result of the introduction of mechanical asynchrony were very similar to those measured in the animal experiments. In conclusion, the module presented describes ventricular mechanics including direct ventricular interaction realistically and thereby extends the physiological application range of the CircAdapt model.

INTRODUCTION

The left (LV) and right ventricle (RV) of the heart are pumping blood in the systemic and pulmonary circulation, respectively. Although both ventricular cavities are completely separated, there is a strong mechanical interaction between the ventricles, because they share the same septal wall, separating the cavities. A vast amount of evidence demonstrates that septal shape and motion depend on transseptal pressure.^{7,8} Also, a change in pressure or volume load of one ventricle influences pumping characteristics of the other ventricle.^{4,12,15}

Various mathematical models have been designed to describe the consequences of mechanical left-right coupling by the septum for ventricular geometry and hemodynamics.^{5,6,11,14,16,18} Commonly, interaction is assumed to be global and linear, using coupling coefficients for pressures, volumes or compliances. An exception was found in the model by Beyar *et al.*,⁵ which was based on the balance of forces between free walls and septum. The latter model was primarily designed for diastolic interaction and was not suited to implement the dynamic mechanics of myocardial contraction.

The CircAdapt model³ has been developed to simulate cardiovascular dynamics and hemodynamics of the closed-loop circulation. The model is configured as a network, composed of four types of modules, i.e., cardiac chamber, blood vessel, valve and flow resistance. The number of required independent input parameters was reduced tremendously by incorporating adaptation of geometry, e.g., size of ventricular cavities and thickness of walls, to mechanical load so that stresses and strains in the walls were normalized to physiological standard levels. Ventricular interaction was modeled as an outer myocardial wall, encapsulating both ventricles, and an inner wall around the LV cavity accommodating the pressure difference between LV and RV. This description is reasonable, as long as LV pressure largely exceeds RV pressure. However, for high RV pressures, the description is not accurate anymore.

Because of the need to describe pathologic circumstances with high RV pressure, a new model of left to right ventricular interaction was designed. This model should be symmetric in design, allowing RV pressure to exceed LV pressure. Furthermore, the new model should satisfy the following requirements to fit in the CircAdapt framework. 1) For given LV and RV volumes as input, LV and RV pressures should be calculated as a result. 2) The model should incorporate dynamic myofiber mechanics, responsible for pump action. 3) The model should satisfy conservation of energy, i.e., the total amount of contractile work, as generated by the myofibers, should equal the total amount of hydraulic

pump work, as delivered by the ventricles.

In the present study, a model setup was found, satisfying abovementioned requirements. The LV and RV cavities are formed between an LV free wall segment and a septal wall segment and between the septal wall segment and an RV free wall segment, respectively. The area of each wall segment depends on myofiber length in that wall. Pressures are generated by wall tension in the curved wall segments. Equilibria of mechanical forces are used to restrict degrees of freedom for geometry.

The model was tested by manipulating timing of mechanical activation of the various wall segments. Consequences of left bundle branch block (LBBB) have been simulated for septal motion and timing of LV and RV pressure development. Model results were compared with experimental results reported earlier.^{1,8-10,13,20}

METHODS

Model design

In the model, LV and RV cavities are enclosed by an LV and an RV free wall segment (LVfw and RVfw, respectively). The cavities are separated by a shared septal wall segment (Sept) (*Figure 3.1*). The wall segments are modeled as thick-walled spherical segments. The segments are assumed to be mechanically coupled at midwall. Midwall surface is defined to divide the wall in two spherical shells of equal wall volume. Midwall geometry of a wall segment depends on two variables, i.e., the midwall bulge height of the spherical segment ($x_{m,Sept}$), and the radius of the midwall boundary circle (y_m) (*Figure 3.1*). Midwall curvature, area, and volume of a wall segment can be expressed as a function of these two variables. Since all three wall segments share the same circle of intersection, four variables are needed to describe complete ventricular geometry, i.e., $x_{m,RVfw}$, $x_{m,Sept}$, $x_{m,LVfw}$, and y_m .

The core of the CircAdapt model is a set of first-order differential equations describing state-variables such as ventricular cavity volumes and flows through cardiac valves as a function of time.³ The CircAdapt model requires that RV and LV cavity pressures are expressed as function of the related cavity volumes. Since in the new model ventricular geometry is defined by four parameters, and only two volumes are known as input values, two remaining geometric parameters have to be solved. This is done by stating equilibrium of forces in the intersection of the wall segments. In *Figure 3.2*, the sequence of calculations within the ventricular module is shown graphically.

Figure 3.1: A cross-section of the model of ventricular mechanics. Three thick-walled spherical segments (shaded), i.e., the LV free wall segment (LVfw), the RV free wall segment (RVfw), and the septal wall segment (Sept) are coupled mechanically. The resulting ventricular composition is rotationally symmetric around axis x and has a midwall intersection circle crossing this image plane perpendicularly through the thick points. Midwall geometry of the septal wall segment is expressed by bulge height ($x_{m,Sept}$) and the radius (y_m) of the midwall intersection circle. In this intersection each wall segment exerts a force (F) caused by wall tension.

Figure 3.2: Flowchart of the new ventricular module (shaded area), describing ventricular mechanics up to and including the level of the myocardial tissue, as implemented within the framework of the CircAdapt model of the cardiovascular system.³ Ventricular pressures are calculated as a function of cavity volumes. Degrees of freedom in septal geometry are solved by achieving balance of forces. Then, ventricular cavity and wall mechanics as well as sarcomere mechanics are known.

Starting with LV and RV volumes and an estimate of septal bulge height $x_{m,Sept}$ and radius y_m of the intersection circle, for all three segments, bulge height and segment radius are calculated. Next, for each segment, midwall area and curvature is calculated. From midwall area and curvature, sarcomere extension is calculated. Myofiber stress is calculated with constitutive equations of the sarcomere incorporating Hill's sarcomere force-velocity relation and Starling's sarcomere length-contraction relation, as previously described in detail by Arts *et al.*³ Using segment geometry, total radial and axial force components of midwall tension acting on the intersection circle are calculated. Thus, force balance provides two equations, which are solved numerically by proper variation of $x_{m,Sept}$ and y_m . Finally, a solution for ventricular geometry is found and LV and RV pressures are calculated from wall tensions, as needed for the CircAdapt model (Figure 3.2).

Simulation methods

The model was tested by simulating canine ventricular hemodynamics and mechanics. The first simulation (Control) was assumed to be representative for baseline conditions with synchronously contracting ventricular wall segments. In a simulation of left bundle branch block (LBBB) we imposed asynchronous mechanical activation of the three wall segments, similar to that as observed in dogs with LBBB.¹⁹

Table 3.1 shows major input parameters used for the Control simulation, representing normal cardiac loading conditions of a dog.^{20,21} The thickness and midwall area of each wall segment were adapted to the loading conditions by using adaptation rules.³ The LBBB simulation represents an acute experiment in which no structural adaptation has occurred. Thus, with LBBB, size and weight of the wall segments were the same as in Control. Mechanical activation of the septum and LV free wall were delayed by 30 ms and 70 ms relative to the RV free wall, respectively. These average delay times were derived from animal experiments on mongrel dogs in which acute LBBB was induced by ablating the left branch of the His bundle using a radiofrequency catheter.^{20,21}

Table 3.1. Input parameter values used for the simulations.

Parameter	Unit	Value
Mean arterial blood pressure	kPa	10.8
Cardiac output	ml/s	60
Cardiac cycle time	ms	760
Blood pressure drop over pulmonary circulation	kPa	1.33

The set of differential equations has been solved numerically using the ODE113 function in Matlab 7.1.0 (MathWorks, Natick, MA) with a temporal resolution of 2 ms. Simulation results were compared with experimental results of LV and RV pressure curves and the time course of septal motion.

RESULTS

Simulation results of LV and RV hemodynamics for control and LBBB are shown in *Figure 3.3*. In the Control simulation, the time courses of pressures, volumes and flows are within the normal physiological range. In case of LBBB, the following hemodynamic changes, indicated by numbers in *Figure 3.3*, were noted:

1. LV pressure rise and decay were delayed with respect to that of RV pressure
2. Amplitude of the maximum positive time derivative of LV and RV pressures were both decreased.
3. At the beginning of systole RV pressure exceeds LV pressure.
4. Beginning and end of LV ejection occur later than the corresponding RV events.
5. Mitral flow reverses after atrial contraction

Figure 3.3: Time courses of left (LV) and right (RV) ventricular hemodynamics as simulated with the CircAdapt model in Control (left column) and with left bundle branch block (LBBB, right column). From top to bottom: LV and RV pressures, LV and RV volumes, septum-to-free wall distance (SFWD) for the LV and RV, flows through aortic (AoV) and mitral valves (MiV), and flows through pulmonary (PuV) and tricuspid valves (TrV). Encircled numbers correspond to changes listed in the text.

In *Figure 3.3*, septal-to-free wall distances (SFWD) for both ventricles show also characteristic differences between Control and LBBB. In Control, time courses of RV and LV SFWD follow those of RV and LV volumes quite closely. With LBBB, the septum moves leftward during rise of RV pressure, and rightward shortly thereafter. During the rest of the cardiac cycle septal motion is similar in Control and LBBB.

Figure 3.4 shows LV and RV pressure curves normalized to their maximum value. The top panels show these normalized pressures, as obtained experimentally in a dog before and after induction of LBBB.²⁰ The bottom panels show the corresponding simulated curves. Experiment and simulation are in close agreement on the points already mentioned in relation to *Figure 3.3*. Moreover, in *Figure 3.4*, experiment and simulation appear in agreement on the increase of asymmetry of the RV pressure curve with LBBB.

Figure 3.4: Left ventricular (LV) and right ventricular (RV) pressures normalized to their maxima. Top panels: representative experimental results of LV and RV pressures acquired before (Control) and after (LBBB) ablation of the left branch of the His-bundle in dogs. [Adapted from Verbeek *et al.*²⁰] Bottom panels: normalized pressures obtained from the simulations shown in *Figure 3.3*.

Figure 3.5 shows LV SFWD as derived from typical M-Mode echocardiograms acquired in a dog before (Control) and after induction of LBBB.⁹ During LBBB, the experimental LV SFWD curve shows the same typical motion pattern of the septum early in systole as seen in the LBBB simulation.

Figure 3.5: Left ventricular septal-to-free wall distance (LV SFWD) as derived from M-Mode echocardiograms of the left ventricle (LV) in the dog. [Adapted from Liu *et al.*^{9]} The septal wall and LV free wall are indicated by Sept and LVfw, respectively. The left panel was acquired with synchronously contracting ventricles (Control) and the right image after induction of left bundle branch block (LBBB). Start of the QRS complex is indicated by vertical dashed lines. The arrows indicate the early systolic leftward motion of the septum, followed by the paradoxical rightward motion. The simulated curves of LV SFWD, as shown in the bottom panels, appear similar.

Figure 3.6 shows simulated LV and RV pressure-volume loops and myofiber stress-strain loops of all three wall segments. Stroke volumes do not change because cardiac output and heart rate were fixed in both simulations. In the LBBB simulation, the LV pressure-volume loop is shifted rightward, indicating ventricular dilatation that is generally considered representative for loss of cardiac contractile function. The areas of the stress-strain loops indicate contractile work of the myofibers per unit of tissue volume in the different wall segments. In Control circumstances, myocardial stroke work per unit of tissue volume is similar in all three segments, i.e., 5.5, 4.7, and 4.6 kPa for LV free wall, septal wall, and RV free wall, respectively. With LBBB, the early activated RV free wall generates clearly less work per unit of tissue volume (4.2 kPa) than the late activated LV free wall (7.8 kPa). Although the septum is later activated than the RV free wall, the septal tissue generates far less work (0.9 kPa).

Figure 3.6: Simulated pressure-volume loops of the left ventricular (LV) and right ventricular (RV) cavities (top panels) and myofiber Cauchy stress-natural strain loops of the left ventricular free wall (LVfw), septal wall (Sept), and the right ventricular free wall (RVfw) (bottom panels). The left panels show results of the Control simulation and the right panels that of the LBBB simulation.

DISCUSSION

A lumped module was designed, describing ventricular mechanics with direct ventricular interaction. The ventricular cavities were considered to be formed between three wall segments, being the LV free wall, septum and RV free wall. Mechanical interaction between the walls caused mutual dependency of LV and RV pump function. The three-segment ventricular module was incorporated in the closed-loop CircAdapt model of the complete circulation. Size and weight of the constituting wall segments were determined by adaptation of the myocardial tissue to imposed mechanical load. A comparison with experimental data^{9,13,20} demonstrated that simulation results of ventricular mechanics and hemodynamics at baseline and LBBB conditions were surprisingly realistic.

In the model, the atrioventricular valves could close only when the following two conditions were satisfied: 1) ventricular pressure exceeded atrial pressure and 2) the distal ventricular wall segments were mechanically activated. The latter condition mimicked papillary muscle function preventing valvular prolapse when ventricular pressure exceeded pressure in the proximal atrium. In

the LBBB simulation, mitral backflow occurred because LV pressure rose above left atrial pressure before mechanical activation of the LV free wall. As soon as the LV free wall was activated, the mitral valve closed. Patient studies have shown that LBBB patients often have mitral regurgitation possibly as a result of late activation of papillary muscles.¹⁷

Figure 3.6 showed remarkable changes in the amount of myofiber work done by early and late activated wall segments of the LV. The same qualitative changes in LV regional myofiber work density have been observed in animal experiments in which regional LV pump work was derived from strain analysis of short-axis MR tagging images and simultaneous invasive pressure measurements.¹³ In chronic LBBB, these regional differences in work density may be responsible for asymmetric remodeling of the LV wall.²¹

A crucial step in the calculation procedure was the estimation of sarcomere extension. The one-fiber model by Arts *et al.*,² related sarcomere extension to the ratio of cavity volume to wall volume. This model has previously been shown to be applicable to an anisotropic thick-walled structure like a myocardial wall when assuming rotational symmetry and homogeneity of mechanical load in the wall. In our new model, the relation between midwall area and sarcomere extension was derived by applying the one-fiber model to a closed spherical cavity. The resulting relation was then extended to a partial segment of the sphere by considering a fraction of the wall, having the same curvature, wall tension, and transmural pressure difference. The one-fiber model has been shown to be rather insensitive to wall geometry.² We expected the present relation between midwall area, curvature, and transmural pressure also to be quite insensitive to actual geometry. However, this fact has not been proven.

The simulation results demonstrated that ventricular interaction through the septum is one very important mechanism for the hemodynamic changes associated with abnormal mechanical activation of the ventricular wall segments. However, another important potential mechanism might be changes in contractility due to asynchronous contraction within each wall segment. Due to its lumped character, this model did not allow description of regional interactions within each wall segment but was limited to the description of its average sarcomere mechanics.

Experimental data show a decrease of cardiac output by approximately 30% after induction of LBBB.^{20,21} In our simulations, however, cardiac output was the same in the Control and LBBB simulations. In the model, cardiac output affects the forces in the intersection of the three wall segments proportionally, provided LV and RV stroke volumes are the same. Thus, a change of cardiac

output as observed in the experiments will only affect the amplitude of septal wall motion (*Figure 3.5*) but not its characteristic course in time.

The mechanical coupling of the three spherical wall segments resulted in a circle of intersection with two degrees of freedom, namely, radial and axial displacement. This ventricular composition resulted in simple equations relating wall segment geometry to sarcomere behavior. Implementation of this ventricular module in the CircAdapt model resulted in a closed-loop system model that related fiber mechanics within the cardiac and vascular walls to hemodynamics realistically. Calculation time was limited to 6 seconds per cardiac cycle on a regular personal computer. Furthermore, the model behaved symmetrically around zero septal curvature, so that inversion of transseptal pressure and septal bulging could be handled. In conclusion, the resulting ventricular module satisfied all requirements mentioned in the introduction.

CONCLUSION

In the lumped CircAdapt model of the complete circulation, a new module was incorporated, representing the heart with realistic left to right ventricular interaction. The ventricular part of the heart was designed as a composition of the LV free wall, the septum, and the RV free wall, encapsulating the LV and RV cavities. In a test simulation, ventricular hemodynamics and septal motion during normal synchronous activation was compared with these variables during left bundle branch block. Simulated time courses of ventricular pressures and septal motion were in close agreement with experimental findings. The newly developed three-segment module, describing ventricular mechanics with direct ventricular interaction, is a promising tool for realistic simulation of right heart function and septal motion under normal as well as pathologic circumstances, using the framework of the CircAdapt model.

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Chapter 4

Three-Wall Segment (TriSeg) Model Describing Mechanics and Hemodynamics of Ventricular Interaction

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ABSTRACT

A mathematical model (TriSeg model) of ventricular mechanics incorporating mechanical interaction of the left and right ventricular free walls and the interventricular septum is presented. Global left and right ventricular pump mechanics were related to representative myofiber mechanics in the three ventricular walls, satisfying the principle of conservation of energy. The walls were mechanically coupled satisfying tensile force equilibrium in the junction. Wall sizes and masses were rendered by adaptation to normalize mechanical myofiber load to physiological standard levels. The TriSeg model was implemented in the previously published lumped closed-loop CircAdapt model of heart and circulation. Simulation results of cardiac mechanics and hemodynamics during normal ventricular loading, acute pulmonary hypertension, and chronic pulmonary hypertension (including load adaptation) agreed with clinical data as obtained in healthy volunteers and pulmonary hypertension patients. In chronic pulmonary hypertension, the model predicted right ventricular free wall hypertrophy, increased systolic pulmonary flow acceleration, and increased right ventricular isovolumic contraction and relaxation times. Furthermore, septal curvature decreased linearly with its transmural pressure difference. In conclusion, the TriSeg model enables realistic simulation of ventricular mechanics including interaction between left and right ventricular pump mechanics, dynamics of septal geometry, and myofiber mechanics in the three ventricular walls.

GLOSSARY OF TERMS

General

LV	Left ventricle / ventricular
RV	Right ventricle / ventricular
LVfw	Left ventricular free wall
Sept	Septal wall
RVfw	Right ventricular free wall

Geometry-related parameters

V_{LV}	m^3	Left ventricular cavity volume
V_{RV}	m^3	Right ventricular cavity volume
V_w	m^3	Wall volume of ventricular wall segment
V_m	m^3	Volume of spherical cap, formed by midwall surface of wall segment
A_m	m^2	Midwall surface area of curved wall segment
C_m	m^{-1}	Curvature of midwall surface (reciprocal of radius)
x_m	m	Maximal axial distance from midwall surface to origin
y_m	m	Radius of midwall junction circle
z	-	Ratio of wall thickness to midwall radius of curvature of curved wall segment
α	-	Half the opening angle of spherical midwall surface
ϵ_f	-	Natural myofiber strain

Force-related parameters

p_{LV}	Pa	Left ventricular cavity pressure
p_{RV}	Pa	Right ventricular cavity pressure
p_{Trans}	Pa	Transmural pressure difference across curved wall segment
σ_f	Pa	Cauchy myofiber stress
T_m	Nm^{-1}	Representative midwall tension
T_x	Nm^{-1}	Axial midwall tension component
T_y	Nm^{-1}	Radial midwall tension component

INTRODUCTION

The left (LV) and right (RV) ventricular cavities of the normal human heart are separated from the intrathoracic space by the left and right ventricular free walls, respectively (*Figure 4.1A*). The cavities are mutually separated by the septal wall. In order to simulate LV and RV mechanics and hemodynamics, the close anatomic coupling between these two ventricles must be considered. Experimental data demonstrate that a change in loading condition of either ventricle directly influences pump function of the other ventricle.^{5, 21, 50, 55, 68} It is also well recognized that septal geometry and motion depend on transseptal pressure difference.^{36, 37, 51} This dependency is best illustrated by flattening of the septum with increase of RV pressure relative to LV pressure (*Figure 4.1B*). Septal geometry and motion appeared to be of diagnostic and predictive significance in patients with pulmonary hypertension.^{32, 35}

Several mathematical models of ventricular mechanics have been developed to quantify the effect of ventricular interaction on cardiac function. In several lumped models of ventricular hemodynamics,^{7, 13, 41, 43, 48, 53, 56, 60, 61} ventricular interaction is described by empirically determined coupling coefficients, quantifying interventricular cross-talk of pressures and volumes. The model designed by Beyar *et al.*⁷ describes ventricular interaction in a more mechanistic way. In this model, LV and RV cavities are enclosed by three ventricular walls. For given ventricular pressures, the mechanical equilibrium of tensile forces in the junction of the walls is used as constraint to predict ventricular geometry. The model is restricted to description of passive mechanics of walls lacking contractile myofiber properties. More recently, 3D finite element models of the cardiac ventricles were used to simulate ventricular pump function and local tissue mechanics,^{34, 47, 66} inherently including ventricular interaction via the septum. In comparison with lumped models of global ventricular mechanics, finite element models allow description of regional wall mechanics and geometry. Consequently, these models are computationally demanding.

For study of beat-to-beat hemodynamics and mechanics of heart and blood vessels, Arts *et al.* previously developed the closed-loop CircAdapt model of heart and circulation.³ In this model, mechanical interaction of the LV and RV has been simulated by a common outer wall, having a transmural pressure equal to RV pressure, encapsulating an inner wall, which represents the left ventricle.¹ The inner wall encapsulates the LV cavity only and has a transmural pressure equal to the difference between LV and RV pressure. Under normal ventricular loading conditions, this model enables realistic simulation of global LV and RV

pump mechanics.^{1,3} However, this model setup presumes RV pressure to be substantially lower than LV pressure during the whole cardiac cycle. This condition is not satisfied with pulmonary hypertension or with left-to-right asynchrony of electrical activation. Furthermore, septal geometry can not be simulated. Thus, this model can not be used to interpret this measurable signal that contains important information about the difference between LV and RV pressure.^{35, 51} Therefore, we designed the TriSeg model of ventricular mechanics that realistically incorporates ventricular interaction via the interventricular septum.

In the TriSeg model, three wall segments, i.e., the LV free wall (LVfw), septal wall (Sept), and RV free wall (RVfw), meet in a junction margin, thus encapsulating the LV and RV cavities (*Figure 4.2A*). LVfw and RVfw geometries are calculated starting from an initial estimate of Sept geometry. For each wall segment, myofiber strain is calculated from midwall surface area relative to a reference area. From myofiber strain, myofiber stress is determined using constitutive equations describing sarcomere mechanics. Substitution of myofiber stress in the known geometry of the walls results in representative midwall tension, acting on the junction line. Next, septal geometry is adjusted so that equilibrium of tension is achieved, i.e., summed tension at the junction of the three walls is equal to zero. As a result, geometries of the three wall segments and the two cavities are known, together with stresses, tensions, and pressures.

The TriSeg model of ventricular mechanics is designed to be incorporated as a module in the existing CircAdapt model simulating mechanics and hemodynamics of the whole circulation.³ According to the principles of CircAdapt, size and mass of the wall segments are determined by adaptation so that mechanical load of the myofibers is normalized to physiological standard levels.^{3,4} The TriSeg model, as integrated in the CircAdapt model, has been tested by simulation of time-dependent LV and RV mechanics and hemodynamics under normal ventricular loading conditions as well as with acute and chronic pulmonary hypertension (PH). PH has been simulated to test whether the TriSeg model realistically relates septal geometry to transseptal pressure. Simulation results have been compared with previously published experimental data on ventricular hemodynamics^{9,62} and on the relation between septal geometry and transmural pressure^{17,51} in healthy volunteers and in patients with chronic PH.

Figure 4.1: Two typical 2D echocardiographic images showing end-diastolic parasternal short-axis views of the hearts of a normal individual (**A**) and a pulmonary hypertension patient (**B**). Note that the septum is flattened with pulmonary hypertension. Cross-sections of left (LV) and right (RV) ventricular cavities, LV free wall (LVfw), septal wall (Sept), and RV free wall (RVfw) are indicated. The bright dots indicate the cross-section of the junction margin of the walls. In the right upper corner, image plane orientation (shaded plane) is indicated in a schematic representation of the cardiac ventricles.

METHODS

General design of the TriSeg model

The design of the new TriSeg model of ventricular mechanics should enable incorporation as a module in the existing CircAdapt model that simulates mechanics and hemodynamics of the whole circulation.³ Therefore, the TriSeg model calculates LV and RV pressures (p_{LV} and p_{RV} , respectively) as functions of LV and RV cavity volumes (V_{LV} and V_{RV} , respectively). Mechanics of ventricular interaction is incorporated assuming a simplified ventricular composite geometry (*Figure 4.2A*). The three ventricular walls LVfw, Sept, and RVfw are modeled to be thick-walled and spherical with a common junction circle with midwall radius y_m (*Figure 4.2B*). Midwall is defined as the spherical surface that divides wall volume V_w in an inner and an outer shell of equal volume. Midwall volume V_m is the volume enclosed by the midwall surface and the plane of the junction circle (*Figure 4.2C*). The center of the junction circle is the origin of the applied cylindrical coordinate system (*Figure 4.2B*). The x-direction is perpendicular to the plane of the junction circle and is defined positive towards the RV free wall. The y-coordinate represents the radial distance to the x-axis. The spherical midwall surface of a wall segment intersects the x-axis at value x_m (*Figure 4.2C*).

Figure 4.2: TriSeg model of ventricular mechanics. **A:** The TriSeg model (grey shading) incorporated in the modular CircAdapt model of the systemic (syst) and pulmonary (pulm) circulations.³ Three thick-walled spherical segments representing LV free wall (LVfw), RV free wall (RVfw), and septal wall (Sept) form a ventricular composite consisting of a left ventricular (LV) cavity, with volume V_{LV} and pressure p_{LV} , and a right ventricular (RV) cavity, with volume V_{RV} and pressure p_{RV} . **B:** Cross-section of the ventricular composite through the axis of rotational symmetry (x). The ventricular walls are coupled mechanically at the common junction circle where their midwall surfaces (thick lines) meet. This junction circle perpendicularly intersects the plane of drawing (open dots). The midwall surface divides the wall with wall volume V_w in two shells of equal volume. The center of the junction circle is the origin (**0**) of the cylindrical coordinate system applied. Note that x -direction is defined positive towards the RV free wall. **C:** Cross-section of a single wall segment through the axis of rotational symmetry. Note that only midwall geometry is shown. The shaded area indicates midwall volume V_m enclosed between the midwall surface and the junction plane. Midwall volume V_m , area A_m , and curvature C_m (reciprocal of radius of curvature) depend on distance x_m and radius y_m of the boundary circle. Each wall is loaded by transmural pressure difference resulting in a representative midwall tension T_m . With half opening angle α , T_m is resolved in an axial (T_x) and a radial (T_y) component.

In presenting the TriSeg model, the following levels are distinguished, 1) ventricular hemodynamics, 2) ventricular composite mechanics, 3) ventricular wall segment mechanics, 4) curved wall patch mechanics, and 5) myofiber mechanics. Starting from LV and RV volumes, the sequence of calculations needed to obtain LV and RV pressures has been illustrated in *Figure 4.3*. The ventricular hemodynamics section serves as interface with the CircAdapt model of the whole circulation.³ In the ventricular composite section, LV and RV volumes are used to calculate LV and RV pressures, applying a model of wall mechanics to each ventricular wall segment. In the ventricular wall segment section, volume V_m and boundary radius y_m of a spherical wall segment are used to calculate the axial and radial vector components T_x and T_y , respectively, at the common junction circle from representative midwall tension T_m , applying a model of the mechanics of a curved wall patch. Such patch is defined as a fraction of a spherical wall segment with an arbitrarily shaped boundary and with midwall area A_m and curvature C_m . Curvature is defined as the reciprocal of radius of curvature, having the advantage of being well-defined for a flat wall. In the section of curved wall patch mechanics, A_m and C_m are used to calculate representative midwall tension T_m , applying a model of myofiber mechanics. In the myofiber mechanics section, natural myofiber strain ε_f is converted to Cauchy myofiber stress σ_f , using a constitutive law of the myofiber. This model of myofiber mechanics has been heuristically obtained from reported physiological experiments.

Figure 4.3: Flowchart of the TriSeg model of left (LV) and right (RV) ventricular mechanics. Applied equation numbers are indicated. The ventricular hemodynamics section serves as interface with the CircAdapt model of the whole circulation. In the ventricular composite section, for each wall i , midwall boundary radius ($y_{m,i}$) and midwall volume ($V_{m,i}$) are calculated from LV and RV volumes (V_{LV} and V_{RV} , respectively) and septal geometry. Septal geometry is initially defined by estimates of boundary radius ($y_{m,est}$) and midwall volume ($V_{m,Sept,est}$). LV free wall, septum, and RV free wall are indicated by $i = \text{LVfw}$, Sept , and RVfw , respectively. The first dashed arrow indicates calculation of axial ($T_{x,i}$) and radial ($T_{y,i}$) wall tension components and transmural pressure ($p_{Trans,i}$). LV and RV pressure (p_{LV} and p_{RV} , respectively) and a new estimate of septal geometry is obtained from the summed axial ($T_{x,Tot}$) and radial ($T_{y,Tot}$) tension components. If septal geometry is sufficiently accurate by iteration, the solution is accepted. Because direct calculation along the dashed arrow is not possible, the sequence of calculations has to follow the solid lines. For each wall segment, midwall area ($A_{m,i}$) and curvature ($C_{m,i}$) are calculated. Wall tension ($T_{m,i}$) is calculated following the second dashed arrow and renders wall tension components and transmural pressure. Again, direct calculation is not possible. Therefore, in the myofiber section, midwall area and curvature are used to calculate myofiber strain ($\epsilon_{f,i}$). Myofiber strain is converted to myofiber stress ($\sigma_{f,i}$) using a model of sarcomere mechanics. Myofiber stress and wall segment geometry are used to calculate wall tension. By cascading the different sections, calculations can be performed sequentially along the pathways marked by solid lines.

Ventricular composite mechanics

In this section, it is shown how cavity volumes V_{LV} and V_{RV} are used to calculate pressures p_{LV} and p_{RV} . For that purpose, a model of ventricular wall segment mechanics is applied that renders axial and radial tension components (T_x and T_y , respectively) from representative midwall tension as a function of the midwall volume (V_m) and junction radius (y_m) of the spherical wall segment. This latter model will be derived in the next section discussing mechanics of the ventricular wall segment.

The geometry of the ventricular composite (*Figure 4.2B and C*) is defined by the common radius y_m of the wall junction and the enclosed midwall cap volumes $V_{m,LVfw}$, $V_{m,Sept}$, and $V_{m,RVfw}$ of the wall segments LVfw, Sept, and RVfw, respectively. Septal midwall volume $V_{m,Sept}$ and junction radius y_m are initially estimated by the solutions as obtained in the preceding time point, i.e., $V_{m,Sept,est}$ and $y_{m,est}$ respectively:

$$y_m = y_{m,est} \quad (4.1)$$

$$V_{m,Sept} = V_{m,Sept,est} \quad (4.2)$$

The latter estimates, together with ventricular cavity volumes V_{LV} and V_{RV} as given directly by the CircAdapt model, render an estimate of ventricular composite geometry. Using the fact that ventricular cavity volume added to half of wall volume V_w of the enclosing wall segments renders the sum of midwall volumes, it is found:

$$V_{m,LVfw} = -V_{LV} - \frac{1}{2}V_{w,LVfw} - \frac{1}{2}V_{w,Sept} + V_{m,Sept} \quad (4.3)$$

$$V_{m,RVfw} = +V_{RV} + \frac{1}{2}V_{w,RVfw} + \frac{1}{2}V_{w,Sept} + V_{m,Sept} \quad (4.4)$$

Note that the sign of midwall volume V_m is positive if wall curvature is convex to the positive x -direction (*Figure 4.2B*). Thus, for a normal heart, the sign is negative for LVfw and positive for RVfw and Sept.

For each wall segment i , $V_{m,i}$ and $y_{m,i}$ are used to calculate axial and radial tension components $T_{x,i}$ and $T_{y,i}$, as well as transmural pressure $p_{Trans,i}$. This is done by applying a model of ventricular wall segment mechanics as discussed in

the next section. The axial tension components of the three wall segments $T_{x,LVfw}$, $T_{x,Sept}$ and $T_{x,RVfw}$ are summed to calculate the net axial tension $T_{x,Tot}$ in the junction. Similarly, the net radial tension $T_{y,Tot}$ in the junction is obtained. The initial estimates of y_m and $V_{m,Sept}$ (Eqs. 4.1 and 4.2) are adjusted numerically so that for the summed tension components it holds:

$$T_{x,Tot}(y_m, V_{m,Sept}) = 0 \quad (4.5.)$$

$$T_{y,Tot}(y_m, V_{m,Sept}) = 0 \quad (4.6)$$

Having solved Eqs. 4.5 and 4.6, and assuming the pressure surrounding the ventricular composite to be zero, for LV and RV pressures it holds:

$$p_{LV} = -p_{Trans,LVfw} \quad (4.7)$$

$$p_{RV} = +p_{Trans,RVfw} \quad (4.8)$$

Note that the minus sign for p_{LV} is caused by the definition of p_{Trans} , which is positive for a negative x-gradient of pressure in the wall segment.

Mechanics of the ventricular wall segment

In this section, it is shown for a wall segment (Figure 4.2C) how V_m and y_m are used to calculate axial and radial midwall tension components T_x and T_y , and transmural pressure p_{Trans} . For that purpose, a model of the mechanics of a curved wall patch is applied. Such curved wall patch is defined as a fraction of a spherical wall segment with midwall surface area A_m and curvature C_m . This latter model renders representative midwall tension from midwall surface area A_m and curvature C_m and will be derived in the next section discussing mechanics of the curved wall patch.

Wall segment geometry is most conveniently described by radius y_m of the junction circle and distance x_m between plane of junction circle and center of midwall surface (Figure 4.2C). V_m , A_m , and C_m depend on x_m and y_m by

$$V_m = \frac{\pi}{6} x_m (x_m^2 + 3y_m^2) \quad (4.9)$$

$$A_m = \pi (x_m^2 + y_m^2) \quad (4.10)$$

$$C_m = \frac{2x_m}{(x_m^2 + y_m^2)} \quad (4.11)$$

First, x_m is calculated from y_m and V_m by solving Eq. 4.9. Second, A_m and C_m are determined with Eqs. 4.10 and 4.11. Next, A_m and C_m are used to calculate representative midwall tension T_m , applying a model of the mechanics of a curved wall patch as discussed in the next section.

At the circular boundary of the midwall surface (Figure 4.2C), geometric parameters x_m and y_m , and midwall tension T_m are used to calculate axial (T_x) and radial (T_y) tension components:

$$T_x = T_m \cdot \sin\alpha \quad \text{with} \quad \sin\alpha = \frac{2x_m y_m}{x_m^2 + y_m^2} \quad (4.12)$$

$$T_y = T_m \cdot \cos\alpha \quad \text{with} \quad \cos\alpha = \frac{-x_m^2 + y_m^2}{x_m^2 + y_m^2} \quad (4.13)$$

The symbol α represents half opening angle of the circular wall segment (Figure 4.2C).

Transmural pressure p_{Trans} equals total axial force. Consequently, p_{Trans} is calculated by multiplying T_x by the ratio of length of the junction contour ($2\pi y_m$) to area of the junction circle (πy_m^2):

$$p_{Trans} = \frac{2T_x}{y_m} \quad (4.14)$$

Mechanics of the curved wall patch

In this section, it is shown how midwall surface area A_m and curvature C_m are used to calculate representative midwall tension T_m . For that purpose, a constitutive model of myofiber mechanics is applied. This latter model renders Cauchy myofiber stress from natural myofiber strain and is presented in Appendix 4.B.

In the ventricular module, originally implemented in the CircAdapt model,³ the one-fiber model developed by Arts *et al.*² was used to relate ventricular pump mechanics, as described by cavity pressure and volume, to myofiber mechanics, as described by myofiber stress and strain. When assembling three wall segments to a ventricular composite with two cavities, contractile function of a wall segment, as described by representative midwall tension and area change, should be put

between mechanics of cavity and myofiber. The following conditions should be satisfied. First, when folding a wall segment to a completely closed spherical surface, the relation between pump mechanics and myofiber mechanics should be equivalent to the equations of the one-fiber model. Second, like in the one-fiber model, where contractile myofiber work equals ventricular pump work, summed pump work of both cavities should be equal to summed work as generated by the three walls. Furthermore, within each wall segment, work as delivered by the wall through wall tension and changes of geometry, should be equal to the work generated by the myofibers.

In *Appendix 4.A*, it is shown that such a model of wall segment mechanics can be found, although the derivation is quite complex. Because the shape of the midwall area is not relevant for the balance of work, the relations are extended to the more general case of a spherical wall patch with arbitrary shape of the boundary. Thus, for a wall patch it is found that natural myofiber strain ε_f depends on midwall surface area A_m and curvature C_m by the following approximation (relative error <1%), as derived in *Appendix 4.A*:

$$\varepsilon_f \approx \frac{1}{2} \ln \left(\frac{A_m}{A_{m,ref}} \right) - \frac{1}{12} z^2 - 0.019 z^4 \quad \text{with} \quad z = \frac{3C_m V_w}{2A_m} \quad (4.15)$$

where $A_{m,ref}$ represents reference midwall surface area. Note that the dimensionless curvature parameter z is closely related to the dimensionless ratio of wall thickness to radius of curvature. With a constitutive model of the myofiber (*Appendix 4.B*), natural myofiber strain ε_f is used to calculate Cauchy myofiber stress σ_f . In *Appendix 4.A*, it is derived how myofiber stress and wall segment geometry are used to calculate representative midwall tension T_m . It holds by approximation (relative error <2%):

$$T_m \approx \frac{V_w \sigma_f}{2A_m} \left(1 + \frac{z^2}{3} + \frac{z^4}{5} \right) \quad \text{with} \quad \sigma_f = f(\varepsilon_f) \quad (4.16)$$

Equations 4.15 and *4.16* represent the first few terms of a Taylor series approximating the analytically derived expressions. These approximations have the advantage of being well-defined for zero curvature. The analytical derivations cannot be used in numerical calculations, because zero by zero division occurs near zero curvature, while the ratio is analytically well-defined.

Implementation of TriSeg model in CircAdapt model

The TriSeg model of ventricular mechanics is incorporated in the existing CircAdapt model of the whole circulation.³ This latter model supplies the required hemodynamic boundary conditions, i.e., LV and RV cavity volumes. The CircAdapt model is designed as a network of modules representing cardiac chambers, valves, large blood vessels, and peripheral resistances. Extended with the TriSeg model, the CircAdapt model allows beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics, e.g., ventricular cavity volumes and pressures, geometries and representative myofiber mechanics of ventricular walls, and flows through valves. An important feature of the existing CircAdapt model is that the number of independent parameters is reduced by incorporating adaptation of cavity size and wall mass of cardiac chambers and blood vessels to mechanical load so that stresses and strains in the walls of heart and blood vessels are normalized to tissue-specific physiological standard levels.

The model was initialized using realistic estimates of wall volume V_w , reference midwall surface area $A_{m,ref}$, and reference sarcomere length $L_{s,ref}$ (*Table 4.1: Parameter values for model initialization*). After model initialization, these parameters will be obtained for each wall segment by load adaptation as described in the next “Simulations” section. The actual parameter values chosen for initialization (*Table 4.1*) are noncritical due to load adaptation. However, for fast convergence to steady state adaptation these estimates were chosen in physiological range.

The set of differential equations that describe the CircAdapt model, including the TriSeg module, was solved by numerical integration with time steps of 2 ms using the ODE113 function in MATLAB 7.1.0 (MathWorks, Natick, MA). Simulation time of a single cardiac cycle was less than 7 seconds on a Windows XP™ platform (version 2002) with a 2.00 GHz Intel® Core™2 Duo T7250 processor and 1 GB of RAM.

Simulations

The TriSeg model, as integrated in the CircAdapt model, was tested by simulation of human ventricular mechanics and hemodynamics with 1) normal ventricular loading conditions (NORM), 2) acute pulmonary hypertension (PHAc), and 3) chronic pulmonary hypertension including adaptation (PHCh). All simulations are presented with similar values of mean systemic blood flow (cardiac output), cardiac cycle time (heart rate), and mean systemic arterial blood pressure, simulating hemodynamics at rest (*Table 4.1: Hemodynamics at rest*).

NORM simulation

The diameter of large blood vessels was assumed to be determined by adaptation to mean chronic circumstances, which state is most closely described by the condition of rest (*Table 4.1: Hemodynamics at rest*). However, geometry of the heart and wall thickness of large blood vessels were considered to be a result of adaptation to a state of moderate exercise, thus simulating the effect of relatively short periods of training by exercise. The applied simulation protocol of adaptation has been described earlier.³ Briefly recapitulating, with resting hemodynamics (*Table 4.1: Hemodynamics at rest*), diameters of the large blood vessels were adapted until mean blood flow velocity reached the set point value (*Table 4.1: Set point values for adaptation*). Next, a moderate state of exercise was simulated by tripling cardiac output and doubling heart rate (*Table 4.1: Interventions with exercise*). Under these circumstances, wall volume (V_w) and reference midwall surface area ($A_{m,ref}$) of all cardiac wall segments were adapted until maximum and minimum sarcomere length as well as maximum passive myofiber stress reached the set point values of adaptation with exercise (*Table 4.1*). Also, wall thickness of the blood vessels was adapted until maximum wall stress was equal to the set point value (*Table 4.1*). Next, hemodynamics were returned to rest conditions and the above-mentioned adaptation protocol was repeated two or three times until steady state geometry was reached (<1% deviation from set point values). In total, finding the steady state adapted NORM simulation required simulation of about 100-200 cardiac cycles.

PHAc and PHCh simulations

The NORM simulation was used as point of departure for simulation of ventricular mechanics and hemodynamics with increased pulmonary resistance. Steady state simulations (PHAc1, PHAc2, and PHAc3), representing increasing degrees of acute pulmonary hypertension, were obtained by acute increase of mean pulmonary arteriovenous pressure drop in three steps without adaptation

(Table 4.1: Interventions with PH simulations). Finally, adaptation was applied to the three steady state PHAc simulations following the same protocol used for the NORM simulation. This resulted in three steady state simulations (PHCh1, PHCh2, and PHCh3, respectively), representing gradually increasing degrees of chronic pulmonary hypertension at rest.

Table 4.1. Input parameter values for NORM and PH simulations

Parameter	Unit	Value
<i>Hemodynamics at rest</i>		
Mean systemic arterial blood pressure	kPa	12.2
Mean systemic blood flow	ml·s ⁻¹	85
Cardiac cycle time	s	0.850
Mean pulmonary arteriovenous pressure drop	kPa	1.5 (NORM)
<i>Interventions with exercise</i>		
Mean systemic blood flow	ml·s ⁻¹	255
Cardiac cycle time	s	0.425
<i>Set point values for adaptation</i>		
Mean flow velocity in large blood vessels (rest)	m·s ⁻¹	0.17
Maximum vascular wall stress (exercise)	kPa	500
Maximum sarcomere length (exercise)	μm	2.2
Minimum sarcomere length (exercise)	μm	1.75
Maximum passive myofiber stress (exercise)	kPa	10 (LVfw), 8 (Sept), 20 (RVfw)
<i>Interventions with PH simulations</i>		
Mean pulmonary arteriovenous pressure drop	kPa	3.0 (PHAc1 and PHCh1), 4.5 (PHAc2 and PHCh2), 6.0 (PHAc3 and PHCh3)
<i>Parameter values for model initialization</i>		
Wall volume (V_w)	ml	75 (LVfw), 40 (Sept), 30 (RVfw)
Reference midwall surface area ($A_{m,ref}$)	cm ²	80 (LVfw), 45 (Sept), 100 (RVfw)
Reference sarcomere length ($L_{s,ref}$)	μm	2.0 (LVfw, Sept, and RVfw)
Septal midwall volume ($V_{m,Sept}$)	ml	42
Radius of midwall junction circle (y_m)	cm	3.3

LVfw, left ventricular free wall; NORM, normal simulation; PHAc, acute pulmonary hypertension simulation; PHCh, chronic pulmonary hypertension simulation; RVfw, right ventricular free wall; Sept, septal wall.

Simulation data analysis

Ventricular pump mechanics and hemodynamics

Simulated time courses of normal (NORM) LV and RV pressures, volumes, and flows were compared with physiological data obtained in normal subjects.^{26, 29, 54, 62, 63} Area of ventricular pressure-volume relation was calculated to quantify ventricular pump stroke work (W_{stroke}) for the LV and RV. Time courses of blood flow velocities through the mitral, aortic, tricuspid, and pulmonary valves were used to study the effects of chronic pulmonary hypertension on ventricular hemodynamics. For comparison with clinical data obtained in healthy subjects and in patients with chronic pulmonary hypertension,^{9,62} several timing parameters of RV hemodynamics were quantified for the NORM and PHCh simulations. RV ejection time (ET) was quantified as the time from pulmonary valve opening to closure, acceleration time of pulmonary flow (AT) as the time from pulmonary valve opening to moment of maximal pulmonary flow velocity, RV isovolumic contraction time (ICT) as the time from tricuspid valve closure to pulmonary valve opening, and RV isovolumic relaxation time (IRT) as the time from pulmonary valve closure to tricuspid valve opening.

Tissue mechanics

Area of myofiber stress-strain relation was calculated to quantify stroke work density (w_{stroke}) for the LVfw, Sept, and RVfw. Stroke work density was defined as contractile myofiber stroke work per unit of tissue volume.

Ventricular wall geometry

End-diastolic wall thicknesses (H_{ed}) were calculated as wall volume divided by end-diastolic midwall surface area. End-diastole was defined as the moment of mitral valve closure. Furthermore, time courses of LVfw, Sept, and RVfw midwall curvatures were used to assess acute and chronic effects of increase of pulmonary resistance on wall curvatures. The relation between septal geometry and the transeptal pressure gradient in the TriSeg model was compared with the relation found in patients with and without chronic pulmonary hypertension.¹⁷ For that purpose, curvature ratio (CR) was calculated as the Sept/LVfw midwall curvature ratio at the moment of aortic valve closure, whereas transmural pressure ratio (PR) was defined as the difference between maximum LV and RV pressures divided by maximum LV pressure.

RESULTS

Simulation of normal physiology (NORM)

Figure 4.4 shows simulated time courses of ventricular cavity pressures and volumes, aortic and pulmonary artery pressures, and flows through arterial and atrioventricular valves under normal ventricular loading conditions (NORM). These time courses show agreement with physiological data on the following aspects: 1) LV and RV cavity pressures and volumes rise at the end of diastole as

Figure 4.4: Simulated time courses of normal (NORM) LV and RV hemodynamics at rest. The bar plot (bottom panel) displays RV and LV ejection, filling, and isovolumic contraction and relaxation periods. Note that simulation duration amounts to one and a half cardiac cycle. Symbols: A, late active ventricular filling wave; E, early passive ventricular filling wave; IC, isovolumic contraction; IR, isovolumic relaxation; LV, left ventricular; p_{ao} , aortic pressure; p_{LV} , left ventricular pressure; p_{pa} , pulmonary artery pressure; p_{RV} , right ventricular pressure; q_{ao} , aortic valve flow; q_{mi} , mitral valve flow; q_{pv} , pulmonary valve flow; q_{tr} , tricuspid valve flow; RV, right ventricular; V_{LV} , left ventricular cavity volume; and V_{RV} , right ventricular cavity volume.

a result of atrial contraction, 2) time courses of mitral and tricuspid valve flows show an early passive filling wave (E) followed by a clearly separated late filling wave (A) resulting from atrial contraction,²⁶ 3) LV and RV end-diastolic volumes are not significantly different,⁵⁴ 4) RV ejection starts earlier and ends later than LV ejection,²⁹ and 5) durations of LV isovolumic contraction and relaxation exceed the corresponding RV time intervals (*Figure 4.4, bottom panel*).^{62,63} Steady state adaptation rendered LVfw, Sept, and RVfw wall volumes of 76, 38, and 31 ml, respectively. Wall thicknesses $H_{ed,LVfw}$ and $H_{ed,Sept}$ were almost equal and three times as large as $H_{ed,RVfw}$ (*Table 4.2*).

Table 4.2. Simulation results: ventricular wall thickness

		NORM	PHAc			PHCh		
Parameter	Unit		1	2	3	1	2	3
<i>End-diastolic wall thickness</i>								
H _{ed,LVfw}	mm	7.9	7.8	7.6	7.3	8.3	8.2	8.3
H _{ed,Sept}	mm	6.8	6.9	7.0	6.9	6.7	6.9	6.5
H _{ed,RVfw}	mm	2.3	2.1	2.0	1.7	3.3	4.2	5.1

H_{ed} , end-diastolic wall thickness; LV, left ventricular; LVfw, left ventricular free wall; NORM, normal simulation; PHAc, acute pulmonary hypertension simulation; PHCh, chronic pulmonary hypertension simulation; RV, right ventricular; RVfw, right ventricular free wall; Sept, septal wall.

Simulations of acute pulmonary hypertension (PHAc)

The upper panel row of *Figure 4.5* illustrates simulated ventricular pressure-volume loops under normal loading conditions (NORM) and with acutely increased pulmonary resistance (PHAc1, PHAc2, and PHAc3). With increasing pulmonary resistance, RV cavity volume, systolic and diastolic RV pressures, mean pulmonary artery pressure, and RV pump work (*Table 4.3*) increased, while LV cavity volume and pump work were relatively unaffected. The middle panel row of *Figure 4.5* shows stress-strain loops of the myofibers in the ventricular wall segments. Acute rise of pulmonary resistance caused increase of RVfw myofiber stress, myofiber strain, and stroke work density, while it caused decrease of LVfw and Sept stroke work densities (*Table 4.3*). The lower panel row of *Figure 4.5* illustrates time courses of LVfw, Sept, and RVfw midwall curvatures. With increasing pulmonary resistance, Sept midwall curvature decreased predominantly during diastole. In the PHAc3 simulation, the septum

even flattened to zero curvature and bulged shortly towards the LV free wall (negative curvature) during early diastole. LVfw and RVfw curvatures appeared relatively insensitive to acute changes of pulmonary resistance. With increasing pulmonary resistance (*Table 4.2*), $H_{ed,RVfw}$ decreased maximally by 26% in PHAc3 relative to NORM, $H_{ed,LVfw}$ decreased maximally by 8%, whereas $H_{ed,Sept}$ increased only 1%.

Figure 4.5: Simulated ventricular pressure-volume loops, myofiber stress-strain loops, and time courses of midwall curvatures under normal (NORM) and acute pulmonary hypertensive (PHAc1, PHAc2, and PHAc3) ventricular loading conditions. Acute increase of pulmonary resistance resulted in RV dilatation, increased RV pump work, increased contractile work density in the RV free wall, and decreased septal midwall curvature. Simulation duration amounts to one cardiac cycle. LV ejection is indicated in the curvature plots. Abbreviations: LV, left ventricular; LVfw, left ventricular free wall; RV, right ventricular; RVfw, right ventricular free wall; and Sept, septal wall.

* Note that the absolute value of LVfw midwall curvature is used for graphical representation, while this curvature is defined to be negative in the TriSeg model.

Table 4.3. Simulation results: pulmonary artery pressures and ventricular work

		NORM	PHAc			PHCh		
Parameter	Unit		1	2	3	1	2	3
<i>Ventricular pump stroke work</i>								
$W_{\text{stroke,LV}}$	Pa·m ³	1.04	1.04	1.03	1.02	1.05	1.04	1.04
$W_{\text{stroke,RV}}$	Pa·m ³	0.22	0.32	0.42	0.51	0.35	0.48	0.61
<i>Stroke work density</i>								
$W_{\text{stroke,LVfw}}$	kPa	9.41	9.54	9.32	8.66	8.88	8.90	8.78
$W_{\text{stroke,Sept}}$	kPa	8.94	8.28	7.54	6.15	9.19	8.66	8.49
$W_{\text{stroke,RVfw}}$	kPa	7.91	11.66	15.94	21.59	8.59	9.13	9.48
<i>Mean pulmonary artery pressure</i>								
p_{pa}	kPa	2.04	3.56	5.11	6.77	3.53	5.00	6.47

LV, left ventricular; LVfw, left ventricular free wall; NORM, normal simulation; PHAc, acute pulmonary hypertension simulation; PHCh, chronic pulmonary hypertension simulation; p_{pa} , mean pulmonary artery pressure; RV, right ventricular; RVfw, right ventricular free wall; Sept, septal wall; w_{stroke} , stroke work density; W_{stroke} , ventricular pump stroke work.

Simulations of chronic pulmonary hypertension (PHCh)

Figure 4.6 illustrates graphs of the same variables as presented in Figure 4.5, but now rendered after adaptation to increased pulmonary resistance (PHCh1, PHCh2, and PHCh3). Like in absence of adaptation, systolic and diastolic RV pressures, mean pulmonary artery pressure, and RV pump work were elevated with chronic pulmonary hypertension (Table 4.3), while LV pump function remained relatively unaffected. In contrast to the PHAc simulations, RV cavity volume decreased 8% in the PHCh3 simulation (Figure 4.6). The myofiber stress-strain loops in Figure 4.6 show that adaptation resulted in a more homogeneous distribution of stroke work density in the ventricular walls (Table 4.3). In the PHCh3 simulation, RVfw stroke work density was increased (20%), whereas LVfw and Sept stroke work densities were decreased (7% and 5%, respectively) relative to the NORM simulation. Increase of pulmonary resistance with load adaptation resulted in the following changes of ventricular geometry. Mean Sept curvature (Figure 4.6) decreased linearly with increasing pulmonary resistance, while the shape of the time course was preserved. LVfw and RVfw curvatures were practically unaffected. Relative to the NORM simulation, $H_{\text{ed,RVfw}}$ increased up to 120% in PHCh3, whereas changes of $H_{\text{ed,LVfw}}$ and $H_{\text{ed,Sept}}$ were small (<5%) (Table 4.2).

In *Figure 4.7*, time courses of LV and RV inflow and outflow velocities are shown for the NORM and PHCh simulations. With increasing pulmonary resistance, pulmonary and tricuspid valve flow velocities changed significantly relative to the NORM simulation, whereas aortic and mitral valve flow velocities remained relatively unaffected. Furthermore, in *Figure 4.7*, RV ejection time (ET),

Figure 4.6: Simulated ventricular pressure-volume loops, myofiber stress-strain loops, and time courses of midwall curvatures under normal (NORM) and chronic pulmonary hypertensive (PHCh1, PHCh2, and PHCh3) ventricular loading conditions. Chronic increase of pulmonary resistance including adaptation resulted in increase of RV pump work, homogeneity of contractile work densities in the walls, and linear decrease of septal midwall curvature. Simulation duration amounts to one cardiac cycle. LV ejection is indicated in the curvature plots. Abbreviations: LV, left ventricular; LVfw, left ventricular free wall; RV, right ventricular; RVfw, right ventricular free wall; and Sept, septal wall.

* Note that the absolute value of LVfw midwall curvature is used for graphical representation, while this curvature is defined to be negative in the TriSeg model.

acceleration time of pulmonary flow (AT), RV isovolumic contraction time (ICT), and RV isovolumic relaxation time (IRT) are indicated for the NORM simulation. In *Figure 4.8*, changes of these timing parameters are compared with the changes as observed in clinical studies among normal individuals and patients with chronic pulmonary hypertension.^{9,62} In the simulations, chronic increase of pulmonary resistance caused decrease of AT and AT/ET-ratio, indicating increase of pulmonary flow curve skewness. This is in accordance with measurements as obtained in patients with chronic pulmonary hypertension.⁹ Furthermore, simulated ICT and IRT lengthened (maximally 163% and 47% in the PHCh3 simulation, respectively). The ratio of total RV isovolumic time (ICT+IRT) to ET almost doubled. Again, the simulated changes were similar to the changes as observed in patients with pulmonary hypertension.⁶² Furthermore, the tricuspid early filling wave narrowed and the tricuspid E/A-ratio of peak atrioventricular flow during early filling (E) to that during atrial contraction (A) decreased from 1.49 in the NORM simulation to unity in the PHCh3 simulation.

Figure 4.7: Simulated time courses of pulmonary and tricuspid valve flow velocities (upper two panels) show lengthening of RV isovolumic contraction, shortening of RV ejection, and increase of pulmonary flow acceleration after adaptation to increased pulmonary resistance (PHCh1, PHCh2, and PHCh3). Aortic and mitral valve flow velocities (lower two panels) appear relatively insensitive to increase of pulmonary resistance. Simulation duration amounts to one cardiac cycle. The following time intervals are indicated for the NORM simulation: AT, acceleration time of pulmonary valve flow; ET, RV ejection time; ICT, RV isovolumic contraction time; and IRT, RV isovolumic relaxation time. Symbols: A, late active ventricular filling wave; and E, early passive ventricular filling wave.

Figure 4.8: Comparison of simulated and patient data on timing of RV hemodynamics. Simulated changes of AT, ET, ICT, and IRT as chronic response to increased pulmonary resistance agree with measurements obtained in healthy normals and patients with pulmonary hypertension [Adapted from Bossone et al.⁹ (upper row) and Tei et al.⁶² (lower row)]. Patient data are presented by mean values with standard deviations indicated by error bars. Symbols: AT, pulmonary flow acceleration time; ET, RV ejection time; ICT, RV isovolumic contraction time; and IRT, RV isovolumic relaxation time.

Figure 4.9: Simulated time courses of Sept/LVfw transmural pressure ratio (upper panel) and Sept/LVfw midwall curvature ratio (lower panel) appear similar revealing a linear relation between both ratios at each time point in the cardiac cycle. Simulation duration amounts to one cardiac cycle. Duration of LV ejection is indicated by vertical dashed lines.

Figure 4.9 shows simulated time courses of Sept/LVfw transmural pressure ratio and Sept/LVfw midwall curvature ratio. Sept transmural pressure was quantified as LV cavity pressure minus RV cavity pressure, while LVfw transmural pressure was quantified as LV cavity pressure. At each time point in the cardiac cycle, both ratios decreased linearly with increase of pulmonary resistance.

Both CR and PR decreased with increase of pulmonary resistance (Table 4.4). Figure 4.10 shows the relation between CR and PR, as derived from the NORM and PHCh simulations, as well as the relation found among patients with and without pulmonary hypertension.¹⁷ In this latter patient population, pulmonary hypertension was defined as an RV systolic pressure >40 mmHg. Linear

Figure 4.10: Simulation results on the correlation between curvature ratio CR and transmural pressure ratio PR (black data points), see text for definitions, as compared with the relation extracted from data (grey data points) obtained in patients with and without pulmonary hypertension (PH = RV systolic pressure >40 mmHg) [Adapted from Dellegrottaglie *et al.*¹⁷]. Linear regression analysis of data points as derived from the NORM and PHCh simulations revealed a strong correlation (bold black line, $r^2=1.00$, $SEE=0.008$) between CR and PR with similar slope as the relation found in patients (thick grey dashed line, $r^2=0.73$, $SEE=0.044$). The thin dashed lines indicate the 95% confidence interval of linear regression fit to the patient data. Linear regression formulas are shown for simulated as well as measured data points. Symbols: r , regression residual; and SEE , standard error of the estimate.

regression analysis of data points as derived from the NORM and PHCh simulations revealed a strong correlation ($r^2=1.00$, $SEE=0.008$) between CR and PR with similar slope as the relation found in patients ($r^2=0.73$, $SEE=0.044$). In the simulations, however, an offset was found, shifting the relation to higher CR values (*Figure 4.10*). It is noted (not shown) that although acute change ($\pm 20\%$) of mean systemic flow or mean arterial blood pressure affected CR and PR, their interdependence followed the linear relation as derived from the chronic simulations within 2% deviation. The same holds for the data points derived from the PHAc1 and PHAc2 simulations, while for the PHAc3 simulation the deviation was more than 10% (*Table 4.4*, not shown in *Figure 4.10*).

Table 4.4. Simulation results: curvature ratio and transmural pressure ratio

Parameter	Unit	NORM	PHAc			PHCh		
			1	2	3	1	2	3
CR	-	0.94	0.85	0.72	0.54	0.81	0.67	0.55
PR	-	0.78	0.68	0.57	0.46	0.65	0.52	0.40

CR, septal-to-LV free wall midwall curvature ratio at the moment of aortic valve closure; NORM, normal simulation; PHAc, acute pulmonary hypertension simulation; PHCh, chronic pulmonary hypertension simulation; PR, systolic septal-to-LV free wall transmural pressure ratio.

DISCUSSION

The newly designed TriSeg model of ventricular mechanics incorporates mechanical interaction of the LV free wall, RV free wall, and septal wall resulting in a strong coupling of LV and RV pump mechanics and hemodynamics. The TriSeg model was successfully implemented as a module in the available CircAdapt model, simulating cardiac mechanics and hemodynamics of the closed-loop circulation. Effects of ventricular interaction on cardiac mechanics and hemodynamics were assessed by simulation of pulmonary hypertension in the acute phase as well as in the chronic phase, the latter implying adaptation of ventricular geometry to mechanical load. For chronic pulmonary hypertension, simulated ventricular geometry, hemodynamics, and septal mechanics agreed surprisingly well with corresponding measurements in patients.

Model assumptions

In the TriSeg model, ventricular geometry was approximated by three thick-walled spherical segments encapsulating the LV and RV cavities (*Figure 4.2A*). In reality, the ventricular cavities are enclosed by truncated ellipsoidal muscular walls and the non-contractile basal sheet with valves.⁵⁸ The simplification to spherical segments without a non-contractile sheet resulted in a general underestimation of ventricular dimensions. Although the fact that there are indications that bending stiffness of the myocardium may be important for simulation of septal geometry,^{7,21} we neglected this effect for simplicity. Despite these inaccuracies, relative changes of dimensions during the cardiac cycle as a result of adaptation were simulated realistically.

In the TriSeg model, myofiber strain was estimated from midwall curvature, area, and wall volume by application of the one-fiber model² to a spherical wall segment (*Eq. 4.15 and Appendix 4.A*). The one-fiber model has been shown to be insensitive to actual wall geometry by assuming conservation of energy and homogeneity of fiber stress in the wall.² So, we expected that the present relation for transmural pressure as a function of midwall surface area and curvature was also applicable to the real, more irregular cardiac geometry, although this fact has not been proven.

The analytically derived dependency of myofiber strain on wall segment geometry (*Eq. 4.A7*) appeared continuous and differentiable around $z=0$. To avoid numerical inaccuracy near zero curvature, because of zero-division, a fourth-order Taylor series approximation (*Eq. 4.15*) was used instead. For similar reasons, *Eq. 4.A4* for midwall tension was also approximated by a fourth-order

Taylor series (Eq. 4.16). Within the physiological range of ventricular geometry, the errors of the approximations as compared to the analytically derived relations were smaller than 1% and 2% for strain and tension, respectively. With respect to total ventricular pump work, total myofiber stroke work was overestimated less than 2.6%, whereas total tensile stroke work at the midwall surface was underestimated less than 0.5%.

In the NORM and PHCh simulations, a load-controlling adaptation mechanism was applied to render size and mass of each wall segment. The applied adaptation rules required prescribed values for maximum and minimum sarcomere lengths and for maximum passive myofiber stress in each wall segment (Table 4.1). Maximum and minimum sarcomere lengths were derived from experiments on isolated cardiac muscle of the rat.^{15,31,64} Maximum passive myofiber stress was chosen as adaptation stimulus because experimental data obtained in dogs with chronic volume overload suggested that end-diastolic myofiber stress and ejection strain were important mechanical stimuli for hypertrophy, while peak systolic myofiber stress appeared irrelevant.²² However, when assuming similar values of maximum passive myofiber stress in the three ventricular walls of the TriSeg model, ventricular geometry did not develop anatomically accurate. Therefore, in our model, we adjusted levels of maximum diastolic stress per wall segment (Table 4.1) so that after adaptation the weight ratios for the walls agreed with findings in healthy volunteers.^{19,28}

In the present study, the external pressure surrounding the LV and RV free walls was assumed to be zero. The real heart is surrounded by the pericardium, which constrains increase of total heart volume during volume overload. Under resting conditions, the pericardium is believed to play a minor role, setting pericardial pressure close to zero.^{42,46,67} However, with acute increase of total heart volume, the pericardium affects cardiac hemodynamics and interaction of the cardiac chambers significantly.^{6,11,25} In our simulations of acute pulmonary hypertension (PHAc), the effect of the pericardium should be considered because of severe RV dilatation (Figure 4.5). In the PHAc3 simulation, RV cavity volume even increased by 120% relative to the NORM simulation. Together with the changes of right atrial and LV cavity volumes (45% increase and 10% decrease, respectively), total heart volume increased by 25%. In the chronic PH simulations, the effect of the pericardium on ventricular mechanics is likely to be of minor importance, because measurements demonstrated adaptive dilatation of the pericardium in patients with chronic pulmonary hypertension.^{8,24}

Comparison of model simulations with measurements

The relation between curvature ratio CR and transmural pressure ratio PR as extracted from the NORM and PHCh simulations (*Figure 4.10*) agreed quite well with the relation as found in a patient group consisting of patients with and without chronic pulmonary hypertension.¹⁷ The relations were about linear with equal slope. In the simulations, however, an offset was found, shifting the relation to higher CR values, implying overestimation of septal curvature for a given right-to-left pressure ratio.

The overestimation of septal curvature may have many causes. In the model, wall geometry was considered spherical having a clear unique radius of curvature by definition. The real ventricular walls are not spherical,⁵⁸ implying that radii of curvature along the circumferential and base-to-apex direction are different. Also, the junction of the real ventricular walls is smoothed over the wall boundaries, thus further hindering a clear definition of curvature. Besides an error in the curvature ratio as derived from the simulations, the offset might originate from a systematic error in the pressure or curvature measurements obtained in patients as discussed by Dellegrottaglie *et al.*¹⁷ Nonetheless, the linear relationship between CR and PR might be a useful tool for noninvasive estimation of systolic RV cavity pressure in patients with RV pressure overload.^{17,35,51} In the simulations, the linear relation appeared also valid (<2% deviation) for the PHAc1 and PHAc2 simulations (*Table 4.4*) as well as after acute changes ($\pm 20\%$) of mean arterial pressure and cardiac output in the chronic pulmonary hypertension simulations (*not shown in Figure 4.10*). The latter findings suggested that the linear relation between CR and PR is insensitive to acute changes of hemodynamic status.

Experimental studies with acute manipulation of transseptal pressure difference as well as clinical studies among patients with chronic pulmonary hypertension showed that septal curvature and position of the septum between the LV and RV free walls depend instantaneously on transseptal pressure difference.^{10,20,21,35,36,52} This dependency was found during systole as well as diastole. Similar dependencies were found in our simulations of pulmonary hypertension. Septal curvature decreased with increase of pulmonary resistance (*Figures 4.5 and 4.6*). Furthermore, leftward shift of the septum, increase of RV volume, and decrease of LV volume with acute increase of pulmonary resistance (*Figure 4.5*), as predicted by the TriSeg model, were also predicted by Kerckhoffs *et al.*³⁴ using a finite element model of the ventricles coupled to a lumped circulation model.

Simulations and clinical observations were in agreement concerning

changes in timing of cardiac flow events due to pulmonary hypertension (*Figures 4.7 and 4.8*). For example, acceleration time of pulmonary flow velocity was significantly decreased and varied linearly with mean pulmonary artery pressure.^{9,14} Furthermore, RV isovolumic contraction and relaxation times increased while pulmonary ejection time decreased.^{62,70} Moreover, tricuspid E/A-ratio was decreased in patients with chronic pulmonary hypertension indicating deterioration of RV diastolic function.⁷¹

Ventricular wall volumes and end-diastolic wall thicknesses (*Table 4.2*) in the NORM simulation were all about 25% smaller than values measured in healthy volunteers.^{19,28,57} This difference most likely resulted from an overestimation of contractility used in the sarcomere mechanics model (*Appendix 4.B, Eq. 4.B7*), causing walls to be thinner after adaptation to mechanical load. Furthermore, pulmonary acceleration and ejection times as derived from the NORM simulation (*Figure 4.8*) were underestimated as compared to data obtained in healthy individuals.^{9,27} A probable cause is inaccuracy in the model description of sarcomere mechanics, which is primarily derived from experiments on isolated cardiac muscle of the rat.^{15,31,64} Human myocardium under *in vivo* conditions is likely to behave differently.

In the PHCh simulations, LV pump function and hemodynamics were relatively unaffected by increase of pulmonary resistance (*Figures 4.6 and 4.7*). Also in rats with chronic pulmonary hypertension, resting LV pump function remains unaffected as long as the myocardium is able to compensate for increased tissue load by structural adaptation.²³ Furthermore, in the PHCh simulations, the RV free wall hypertrophied and RV cavity volume decreased (*Table 4.2 and Figure 4.6*). These geometric changes were in agreement with experimental observations in rats with mild chronic pulmonary hypertension.⁴⁹ In the latter study, chronic pulmonary artery banding resulted in an increase of RV systolic pressure from 33 to 71 mmHg. This increase of RV afterload resulted in 76% increase of thickness of the RV free wall and 14% decrease of RV free wall area, which suggests a small reduction in RV cavity volume. In our simulations, RV systolic pressure increased from 27 mmHg in the NORM simulation to 72 mmHg in the PHCh3 simulation (*Figure 4.6*), end-diastolic wall thickness increased 120% (*Table 4.2*), and RV cavity volume decreased 8%. In another animal study in rats,⁴⁴ it was shown that structural adaptation to chronic increase of RV afterload was associated with concentric hypertrophy up to a certain level. Beyond this level, however, the myocardium could not fully compensate for further load increase. Consequently, the RV cavity dilated, mainly due to dilatation of the RV free wall. In patients with severe chronic

pulmonary hypertension, RV free wall hypertrophy is found to occur together with RV dilatation.^{12,30} Secondary to RV failure, systolic and diastolic LV function deteriorate by ventricular interaction.^{38,39} As a result, cardiac performance deteriorates and exercise capacity reduces.^{12,45} These phenomena indicating RV failure were also found in our PHAc simulations.

In the PHAc simulations, the myocardial tissue was unable to compensate for increased RV afterload by load adaptation. As a result, mechanical myofiber load was inhomogeneously distributed over the ventricular walls (*Table 4.3 and Figure 4.5*). RVfw stroke work density increased with increase of RV afterload, whereas LVfw and Sept stroke work densities decreased. In the PHAc3 simulation, RVfw stroke work density was increased by almost 200% with respect to the NORM simulation. When assuming stroke work density to be correlated to oxygen consumption,⁵⁹ this implies an increase of oxygen demand by the RV free wall. Since oxygen supply is not included in our model, the potential effect of perfusion imposed limitations on myocardial performance is unknown in our simulations of pulmonary hypertension.

In patients with pulmonary hypertension, tricuspid regurgitation often occurs due to RV and tricuspid annular dilatation.^{18,65} In our simulations, tricuspid valve regurgitation was not included. In the PHAc3 simulation, RV end-diastolic volume was increased by almost 100% with respect to the NORM simulation. It is likely that the absence of tricuspid regurgitation resulted in underestimation of RV volume overload in the PHAc simulations.

The TriSeg model was successfully integrated as a module in the CircAdapt model of the closed-loop cardiovascular system. As shown previously, the CircAdapt environment is flexible by its modular setup and enables realistic simulation of cardiovascular mechanics and hemodynamics under normal as well as various pathological conditions.^{3,33,40} A set of physiological adaptation rules, expressing structural adaptation of the system to mechanical load, makes the model self-structuring and reduces the number of independent model parameters. For each ventricular wall segment in the TriSeg model, wall volume, midwall area, and reference sarcomere length were varied so that mechanical myofiber load was normalized to a known physiological level, which was assumed to be the same for all ventricular walls. The field of application of the CircAdapt model was substantially enlarged by implementation of the TriSeg model. In the future, the combined model may be used to study fundamental research questions concerning ventricular interaction and its role in cardiac pathologies. For example, specific material properties may be changed per wall segment in order to study effects of heterogeneity of wall properties on cardiac

mechanics and hemodynamics, e.g., asynchronous mechanical activation (and pacing) or a localized myocardial infarct.^{33,40}

Although the TriSeg model can be easily modified to include a description of inhomogeneous myocardial wall properties, a finite element model of cardiac mechanics is more accurate and better suited to describe local inhomogeneities in mechanical load. For patient-specific modeling of the circulation, the model should simulate many cycles in order to find a best match with the available set of measurements. For that purpose, the TriSeg model is to be preferred because calculation effort was about 1,000 times less than that of a finite element approach. The finite element model is absolutely needed to estimate and evaluate possible errors introduced by the applied simplifications of the TriSeg model. Currently, the CircAdapt model with the TriSeg module will be evaluated in its possibility to simulate hemodynamics of pulmonary hypertension patient-specifically.

CONCLUSIONS

We presented the TriSeg model of ventricular mechanics and hemodynamics incorporating mechanical interaction of the LV free wall, RV free wall, and septal wall, resulting in a strong coupling of LV and RV hemodynamics. The model enables calculation of LV and RV pressures given the respective cavity volumes. LV and RV hemodynamics are related to myofiber mechanics in the three ventricular walls, satisfying the principle of conservation of energy. The three ventricular walls are mechanically coupled satisfying equilibrium of tensile forces in their junction. After implementation as a module in the lumped closed-loop CircAdapt model of heart and circulation, the TriSeg model enables simulation of ventricular hemodynamics and wall mechanics as functions of time.

Simulations of cardiac mechanics and hemodynamics during normal ventricular loading, acute pulmonary hypertension, and chronic pulmonary hypertension after load adaptation agreed with clinical data as obtained in normal subjects and in chronic pulmonary hypertension patients. With increasing levels of chronic pulmonary hypertension, the TriSeg model predicted increase of systolic pulmonary flow acceleration, increase of isovolumic contraction and relaxation times, and linear decrease of septal-to-LV free wall curvature ratio. Summarizing, the TriSeg model realistically describes ventricular mechanics including the interaction between left and right ventricular pump mechanics, dynamics of septal geometry, and contractile myofiber function in the three ventricular walls.

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APPENDIX 4.A: DERIVATIONS OF MECHANICS OF THE CURVED WALL PATCH

This appendix contains the analytical derivations of *Eqs. 4.15 and 4.16* relating mechanics of the curved wall patch to myofiber mechanics. For the derivation of *Eq. 4.16*, calculating representative midwall tension T_m from myofiber stress, the logarithmic one-fiber model relating global ventricular pump mechanics to myofiber mechanics is used.² Applying the definition of midwall surface as used in *Eqs. 4.3 and 4.4*, for the ratio of transmural pressure p_{Trans} to myofiber stress σ_f in a closed thick-walled sphere with midwall volume V_m and wall volume V_w , it holds:

$$\frac{p_{Trans}}{\sigma_f} = \frac{1}{3} \ln \left(\frac{1+z}{1-z} \right) \Big|_{sphere} \quad \text{with} \quad z = \frac{V_w}{2V_m} \Big|_{sphere} \quad (4.A1)$$

where the definition of z is equivalent to the more general definition used in *Eq. 4.15* for a curved wall patch. For a closed sphere with midwall surface area A_m and curvature C_m , the relation between p_{Trans} and representative midwall tension T_m is determined by conservation of energy, i.e.,

$$p_{Trans} dV_m = T_m dA_m \Big|_{sphere} \quad (4.A2)$$

where dV_m and dA_m represent small increments of midwall volume and area, respectively. Substitution of $V_m=4/3\pi r^3$, $A_m=4\pi r^2$, and $r=1/C_m$ in *Eq. 4.A2* yields:

$$p_{Trans} = 2T_m C_m \quad (4.A3)$$

Note that, *Eq. 4.A3* represents Laplace's law expressed in such a way that the applied scalar definition of T_m satisfies conservation of energy (*Eq. 4.A2*). Although we have derived *Eq. 4.A3* for a complete sphere, it also holds for a fraction of the same sphere, since both curvature C_m and tension T_m are local parameters. Thus, *Eq. 4.A3* may also be applied to a spherical wall segment (*Figure 4.2C*). Substituting *Eq. 4.A3* in *Eq. 4.A1* and applying $C_m=(2A_m z)/(3V_w)$ renders for representative midwall tension T_m in a curved wall patch:

$$T_m = \frac{\sigma_f V_w}{2A_m} \cdot \frac{1}{2z} \ln \left(\frac{1+z}{1-z} \right) \quad (4.A4)$$

Note that this latter function is continuous around zero curvature. To avoid numerical inaccuracy near $z=0$, Eq. 4.A4 is replaced by its close fourth-order polynomial approximation as specified in Eq. 4.16 (relative error <2%).

For the derivation of Eq. 4.15, myofiber strain ε_f is considered a function of two variables, i.e., A_m and C_m . Applying the principle of conservation of energy, work of the wall by a small area change dA_m with tension T_m equals work of the myofibers by a change of natural myofiber strain $d\varepsilon_f$ with Cauchy myofiber stress σ_f :

$$T_m dA_m = V_w \sigma_f d\varepsilon_f \quad (4.A5)$$

Rearranging Eq. 4.A5, substituting T_m with Eq. 4.A4, and keeping C_m constant renders the following partial derivative:

$$\frac{\partial \varepsilon_f}{\partial A_m} = \frac{1}{4A_m z} \ln \left(\frac{1+z}{1-z} \right) \quad \text{with} \quad z = \frac{3C_m V_w}{2A_m} \quad (4.A6)$$

A standard mathematical solution technique is used to find the general solution of the first-order partial differential equation in Eq. 4.A6.¹⁶ For that purpose, ε_f is written as the sum of a strain term $\varepsilon_{f,AC}$ and a strain term $\varepsilon_{f,C}$:

$$\varepsilon_f = \varepsilon_{f,AC}(A_m, C_m) + \varepsilon_{f,C}(C_m) \quad (4.A7)$$

First, integration of Eq. 4.A6 with respect to A_m renders strain term $\varepsilon_{f,AC}$ under the condition that C_m remains constant during integration:

$$\varepsilon_{f,AC}(A_m, C_m) = \frac{1}{2} \ln \left(\frac{A_m}{A_{m,ref}} \right) + \frac{1}{4z} \ln \left(\frac{(1+z)^{1+z}}{(1-z)^{1-z}} \right) \quad (4.A8)$$

Symbol $A_{m,ref}$ represents a reference value of midwall surface area A_m . Below, the term $\varepsilon_{f,C}$ will be derived for a relatively simple special case of inflating a closed sphere. The thus found expression is valid for all combinations of A_m and C_m . For a closed thick-walled sphere myofiber strain ε_f is known as a function of V_m . Using the principle that work as generated by the myofibers equals pump work, it holds:

$$V_w \sigma_f d \epsilon_f = p_{Trans} dV_m \Big|_{sphere} \quad (4.A9)$$

Substitution of *Eq. 4.A1* in *Eq. 4.A9* renders for a closed sphere:

$$\frac{d \epsilon_f}{dV_m} = \frac{1}{3V_w} \ln \left(\frac{1+z}{1-z} \right) \Big|_{sphere} \quad (4.A10)$$

Then, midwall volume V_m and curvature ratio z are expressed as functions of curvature C_m :

$$V_m = \frac{4\pi}{3C_m^3} \Big|_{sphere} \quad (4.A11)$$

$$z = \frac{3V_w C_m^3}{8\pi} \Big|_{sphere} \quad (4.A12)$$

Substitution of *Eqs. 4.A11* and *4.A12* in *Eq. 4.A10* results in a differential equation in C_m only. Integration of this differential equation with respect to C_m yields an expression of myofiber strain ϵ_f for a closed sphere as function of C_m (full equation given in *Appendix 4.C*):

$$\epsilon_f = f(C_m) \Big|_{sphere} \quad (4.A13)$$

Applying *Eq. 4.A8* to a closed sphere with curvature C_m and substituting the resulting expression as well as *Eq. 4.A13* in *Eq. 4.A7*, results in the unknown strain term $\epsilon_{f,C}$ (full equation given in *Appendix 4.C*):

$$\epsilon_{f,C}(C_m) = \epsilon_f \Big|_{sphere} - \epsilon_{f,AC}(A_m, C_m) \Big|_{sphere} \quad (4.A14)$$

Finally, substitution of *Eqs. 4.A8* and *4.A14* in *Eq. 4.A7* yields a complicated analytical expression of natural myofiber strain ϵ_f in a curved wall patch (*Appendix 4.C*). Mathematica 5.2 (Wolfram Research, Inc) was used to obtain a simpler fourth-order polynomial fit as specified in *Eq. 4.15*. This latter expression closely approximates the analytical derivation (relative error <1%).

APPENDIX 4.B: MODEL OF MYOFIBER MECHANICS

In this appendix, the applied heuristic relation is presented that converts natural myofiber strain ε_f to Cauchy myofiber stress σ_f . This empirical representation of sarcomere contraction simulates experiments on isolated rat cardiac muscle.^{15,64} Parameter values are given in *Table 4.B*.

Natural myofiber strain is converted to sarcomere length L_s by:

$$L_s = L_{s,ref} e^{\varepsilon_f} \quad (4.B1)$$

The sarcomere has been modeled as a passive element in parallel with a series combination of a contractile element and series elastic element. The time-dependent behavior is described by two state variables, i.e., contractile element length L_{sc} and mechanical activation C . This latter activation parameter is physiologically related to intracellular calcium concentration. The time derivative of L_{sc} depends linearly on length of the series elastic element ($L_s - L_{sc}$) and equals zero for isometric contraction:

$$\frac{dL_{sc}}{dt} = \left(\frac{L_s - L_{sc}}{L_{se,iso}} - 1 \right) v_{max} \quad (4.B2)$$

where v_{max} represents velocity of sarcomere shortening with zero load and $L_{se,iso}$ length of the isometrically stressed series elastic element (*Table 4.B*). Dependence on v_{max} represents the myofiber force-velocity relation so that shortening velocity increases with applied external force.

The time derivative of C is heuristically obtained, having separate terms to describe rise and decay of mechanical activation C :

$$\frac{dC}{dt} = \frac{1}{\tau_R} \cdot C_L(L_{sc}) \cdot F_{rise}(t) + \frac{1}{\tau_D} \cdot \frac{C_{rest} - C}{1 + e^{(L_{sc} - L_{sc,rest})/\tau_D}} \quad (4.B3)$$

Parameters τ_R and τ_D are scaling rise and decay time, respectively (*Table 4.B*). Symbols t and C_{rest} represent time and diastolic resting level of activation, respectively. Functions C_L , F_{rise} , and T describe increase of activation with sarcomere length, rise of mechanical activation, and decrease of activation duration with decrease of sarcomere length, respectively:

$$C_L(L_{sc}) = \tanh\left(4.0(L_{sc} - L_{sc0})^2\right) \quad (4.B4)$$

$$F_{rise}(t) = 0.02 \cdot x^3 (8-x)^2 e^{-x} \quad (4.B5)$$

$$\text{with } x = \min(8, \max(0, t/\tau_R))$$

$$T(L_{sc}) = \tau_{sc} (0.29 + 0.3L_{sc}) \quad (4.B6)$$

where L_{sc0} and τ_{sc} represent contractile element length with zero load and a time factor scaling duration of contraction, respectively (*Table 4.B*).

Active myofiber stress $\sigma_{f,act}$ depends on length of series elastic element, L_{sc} , and C :

$$\sigma_{f,act} = \sigma_{act} \cdot C \cdot (L_{sc} - L_{sc0}) \cdot \frac{L_s - L_{sc}}{L_{se,iso}} \quad (4.B7)$$

In order to simulate the contributions of titin as well as collagen to passive myocardial stiffness,⁶⁹ passive stress $\sigma_{f,pas}$ represents a soft behavior for low myofiber strain and a stiff behavior for large positive strain:

$$\sigma_{f,pas} = \sigma_{pas} \left(36 \cdot \max(0, \epsilon_f - 0.1)^2 + 0.1(\epsilon_f - 0.1) + 0.0025e^{30\epsilon_f} \right) \quad (4.B8)$$

The value of σ_{pas} has been adapted so that at maximum sarcomere length with exercise, passive myofiber stress assumes the maximum value (*Table 4.1: Set point values for adaptation*). Total Cauchy myofiber stress σ_f is the sum of active and passive stress:

$$\sigma_f(\epsilon_f) = \sigma_{f,pas} + \sigma_{f,act} \quad (4.B9)$$

The latter result has been substituted in *Eq. 4.16*.

Table 4.B. Parameter values of the sarcomere mechanics model

Symbol	Unit	Value	Parameter description
C_{rest}	-	0.02	Diastolic resting level of activation
L_{sc0}	μm	1.51	Contractile element length with zero active stress
$L_{s,ref}$	μm	2.0	Reference sarcomere length at zero strain
$L_{se,iso}$	μm	0.04	Length of isometrically stressed series elastic element
V_{max}	$\mu\text{m}\cdot\text{s}^{-1}$	7	Sarcomere shortening velocity with zero load
τ_D	ms	32	Factor scaling contraction decay time
τ_R	ms	48	Factor scaling contraction rise time
τ_{sc}	ms	425	Factor scaling duration of contraction
σ_{act}	kPa	120	Factor scaling active myofiber stress
σ_{pas}	kPa	7	Factor scaling passive myofiber stress

APPENDIX 4.C: POLYNOMIAL SERIES APPROXIMATIONS

The polynomial series approximation given by Eq. 4.15 is obtained from the analytical solution expressing natural myofiber strain in terms of A_m and C_m (Eq. 4.A7) by applying the following steps:

1. Expression of myofiber strain ε_f for a closed sphere (use $A_m=4\pi/C_m^2$) as function of C_m (Eq. 4.A13) yields:

$$\varepsilon_f|_{sphere} = -\ln(C_m) + \frac{\ln(8\pi)}{3} + \frac{G(x)}{6} \quad (4.C1)$$

$$G(x) = \frac{1}{x} \cdot \ln\left(\frac{(1+x)^{1+x}}{(1-x)^{1-x}}\right) \quad (4.C1a)$$

$$x = z|_{sphere} = \frac{3C_m^3 V_w}{8\pi} \quad (4.C1b)$$

2. Applying Eq. 4.A8 to a closed sphere (use $A_m=4\pi/C_m^2$) yields:

$$\varepsilon_{f,AC} \Big|_{sphere} = -\ln(C_m) + \frac{1}{2} \cdot \ln\left(\frac{4\pi}{A_{m,ref}}\right) + \frac{G(x)}{4} \quad (4.C2)$$

Substitution of Eqs. 4.C1 and 4.C2 in Eq. 4.A14 yields for strain term $\varepsilon_{f,C}$:

$$\varepsilon_{f,C} = \frac{\ln(8\pi)}{3} - \frac{1}{2} \cdot \ln\left(\frac{4\pi}{A_{m,ref}}\right) - \frac{G(x)}{12} \quad (4.C3)$$

The thus found expression for $\varepsilon_{f,C}$, which holds for the special case of inflating a sphere, is valid for all combinations of A_m and C_m .

3. Substitution of Eqs. 4.C3 and 4.A8 in Eq. 4.A7 yields the general analytical solution of natural myofiber strain ε_f in a curved wall patch:

$$\varepsilon_f = \frac{\ln(8\pi)}{3} - \frac{1}{2} \cdot \ln\left(\frac{4\pi}{A_{m,ref}}\right) + \frac{1}{2} \cdot \ln\left(\frac{A_m}{A_{m,ref}}\right) - \frac{G(x)}{12} + \frac{G(z)}{4} \quad (4.C4)$$

4. In order to facilitate series approximation, $z=K/A$ and $x=K^3$ are substituted in Eq. 4.C4:

$$\begin{aligned} \varepsilon_f = & \frac{\ln(8\pi)}{3} - \frac{1}{2} \cdot \ln\left(\frac{4\pi}{A_{m,ref}}\right) + \frac{1}{2} \cdot \ln\left(\frac{A_m}{A_{m,ref}}\right) \\ & - \frac{1}{12K^3} \cdot \ln\left(\frac{(1+K^3)^{1+K^3}}{(1-K^3)^{1-K^3}}\right) + \frac{A}{4K} \cdot \ln\left(\frac{\left(1+\frac{K}{A}\right)^{1+\frac{K}{A}}}{\left(1-\frac{K}{A}\right)^{1-\frac{K}{A}}}\right) \end{aligned} \quad (4.C5)$$

with A and K representing normalized area and curvature, respectively:

$$A = \frac{A_m}{\sqrt[3]{9\pi V_w^2}} \quad (4.C5a)$$

$$K = \frac{C_m}{2} \sqrt[3]{\frac{3V_w}{\pi}} \quad (4.C5b)$$

5. The first two terms of Eq. 4.C5 are constant strain offsets and are therefore eliminated from the strain relation, which describes the transition from a reference to a new state with state variables A_m and C_m . Taylor series approximation of this simplified version of Eq. 4.C5 yields:

$$\epsilon_f = \frac{1}{2} \cdot \ln \left(\frac{A_m}{A_{m,ref}} \right) - \frac{K^2}{12A^2} - \frac{K^4}{40A^4} + O(K^6) \quad (4.C6)$$

where $O(K^6)$ represents the higher order terms.

6. It is used that $z=K/A$. Furthermore, the fourth-order polynomial approximation of natural myofiber strain in a curved wall patch (Eq. 4.15) is obtained after slight adjustment of the fourth-order term of Eq. 4.C6 for best accuracy within the whole range of operation ($|z|<0.8$).

The polynomial series approximation given by Eq. 4.16 is obtained from the analytical solution expressing representative midwall tension in terms of A_m , C_m , and σ_f (Eq. 4.A4) by applying the following steps:

1. Substitution of $z=(3C_mV_w)/(2A_m)$ in Eq. 4.A4 yields:

$$\frac{T_m}{\sigma_f} = \frac{1}{6C_m} \ln \left(\frac{2A_m + 3C_mV_w}{2A_m - 3C_mV_w} \right) \quad (4.C7)$$

2. Similarly to what has been done to obtain Eq. 4.C5, A and K are substituted in Eq. 4.C7 to facilitate series approximation:

$$\frac{T_m}{\sigma_f} = \frac{L}{6K} \ln \left(\frac{1 + \frac{K}{A}}{1 - \frac{K}{A}} \right) \quad (4.C8)$$

with

$$L = \frac{1}{2} \sqrt[3]{\frac{3V_w}{\pi}} \quad (4.C8a)$$

3. Taylor series approximation of Eq. 4.C8 yields:

$$\frac{T_m}{\sigma_f} = \frac{L}{3A} + \frac{LK^2}{9A^3} + \frac{LK^4}{15A^5} + O(K^6) \quad (4.C9)$$

where $O(K^6)$ represents the higher order terms, which are neglected in the TriSeg model.

4. Finally, the fourth-order polynomial approximation of representative midwall tension (Eq. 4.16), is obtained by rearranging Eq. 4.C9 and using $z=K/A$.

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Chapter 5

Right Ventricular Free Wall Pacing Improves Cardiac Pump Function in Severe Pulmonary Arterial Hypertension: a Computer Simulation Analysis

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ABSTRACT

In pulmonary arterial hypertension (PAH), duration of myofiber shortening is prolonged in the right ventricular (RV) free wall (RVfw) as compared to that in the interventricular septum and left ventricular (LV) free wall (LVfw). This interventricular mechanical asynchrony eventually leads to right heart failure. We investigated by computer simulation whether, in PAH, early RVfw pacing may improve interventricular mechanical synchrony and, hence, cardiac pump function. A mathematical model of the human heart and circulation was used to simulate LV and RV pump mechanics and myofiber mechanics. First, we simulated cardiovascular mechanics of a healthy adult at rest. Size and mass of heart and blood vessels were adapted so that mechanical tissue load was normalized. Second, compensated PAH was simulated by increasing mean pulmonary artery pressure (mPAP) to 32 mmHg while applying load adaptation. Third, decompensated PAH was simulated by increasing mPAP further to 79 mmHg without further adaptation. Finally, early RVfw pacing was simulated in severely decompensated PAH. Time courses of circumferential strain in the ventricular walls as simulated were similar to the ones measured in healthy subjects (uniform strain patterns) and in PAH patients (prolonged RVfw shortening). When simulating pacing in decompensated PAH, RV pump function was best upon 40-ms RVfw preexcitation, as evidenced by maximal decrease of RV end-diastolic volume, reduced RVfw myofiber work, and most homogeneous distribution of workload over the ventricular walls. Thus, our simulations indicate that, in decompensated PAH, RVfw pacing may improve RV pump function and may homogenize workload over the ventricular walls.

INTRODUCTION

In pulmonary arterial hypertension (PAH), progressive increase of pulmonary vascular resistance causes chronic elevation of right ventricular (RV) pressure. When left untreated, PAH leads to right heart failure and premature death.^{18,24} Several studies showed that morbidity and mortality of PAH patients are determined by the ability of the RV to maintain normal stroke volume and cardiac output.^{6,23}

In PAH, structural remodeling (hypertrophy and dilatation) is limited to the RV free wall (RVfw),^{5,19} suggesting an inhomogeneous distribution of myocardial tissue load. Therefore, local reduction of mechanical load of the RVfw may be another therapeutic option, in addition to conventional reduction of pulmonary vascular resistance.⁸

Marcus *et al.*¹⁷ demonstrated the presence of interventricular mechanical asynchrony in severe PAH patients, evidenced as prolonged duration of shortening and delayed peak shortening in the RVfw as compared to that in the LV free wall (LVfw) and the interventricular septum (Sept). RVfw shortening even continued after pulmonary valve closure and appeared related to leftward septal motion during LV isovolumic relaxation. As a potential treatment, early RVfw pacing was suggested to improve interventricular mechanical synchrony and thereby cardiac pump function.^{2,12,17} This seems logical, because during ventricular pacing, mechanical myofiber work is significantly decreased in early activated regions, whereas it is increased in late activated regions.²¹

In order to explore the idea of RV pacing in PAH, we used a mathematical model¹⁶ to simulate ventricular mechanics and hemodynamics under normal and PAH conditions. The hypothesis was assessed that, in severe PAH, early pacing of the RVfw decreases mechanical myofiber load in the RVfw and thereby improves RV pump function.

METHODS

Model design

For the present study, the TriSeg model,¹⁶ describing ventricular mechanics including mechanical interaction of the ventricular walls, was embodied in the CircAdapt model of the whole circulation.¹

The TriSeg model of ventricular mechanics, previously described in more detail by Lumens *et al.*^{15,16} incorporates mechanical interaction of the LVfw, RVfw, and Sept resulting in realistic coupling characteristics of LV and RV pump mechanics. In short, three thick-walled spherical segments representing the

ventricular walls join in a common junction so that they encapsulate the LV and RV cavity. Given LV and RV cavity volume, area and curvature of the LVfw and RVfw are calculated while assuming an initial estimate of Sept geometry. From wall geometry, representative myofiber strain is calculated for each wall. From myofiber strain, myofiber stress is determined using constitutive equations describing sarcomere mechanics. This latter empirical model incorporates sarcomere properties as derived from experiments on isolated cardiac muscle,^{7,26} i.e., velocity of sarcomere shortening increases with passive stretch, strength of activation increases with sarcomere length, and duration of activation increases with sarcomere length. Using myofiber stress and wall geometry, total radial and axial force components of tension acting on the junction are calculated. Then, septal geometry (initially estimated) is adjusted so that equilibrium of tensional force in the junction is satisfied. As a result, geometries of the three ventricular walls are known, together with myofiber stresses, wall tensions, and ventricular cavity volumes and pressures. Summarizing, the TriSeg model relates global LV and RV pump mechanics to local myofiber mechanics in the three ventricular walls. This relation is based on the principle of conservation of energy, meaning that summed ventricular pump work equals summed mechanical work as generated by the myofibers in the ventricular walls.

The CircAdapt model of the whole circulation¹ creates the required physiological environment (circulatory boundary conditions) for the ventricles as represented by the TriSeg model. The CircAdapt model consists of a network of modules representing myocardial walls, valves, large blood vessels, and peripheral resistances. It allows beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics, e.g., volumes and pressures of the ventricular cavities, geometries and myofiber mechanics of the three ventricular walls, and flows through valves. An important feature of the CircAdapt model is that the number of independent parameters is reduced by incorporating adaptation of cardiac and vascular wall size and wall mass to mechanical load so that stresses and strains in the walls of heart and blood vessels are normalized to tissue-specific physiological standard levels.^{1,16}

Pulmonary peripheral resistance was modeled as a non-linear resistive module connecting the compliant pulmonary arterial and venous blood vessels. Pulmonary flow was proportional to the squared pulmonary arteriovenous pressure drop, which was prescribed for each simulation in the present study. This relation is in agreement with the pressure-flow relationship as measured in the human and canine lung with normal as well as increased peripheral pulmonary resistance due to pulmonary vascular disease.^{11,14,28}

Simulations

Cardiovascular mechanics and hemodynamics were simulated under normal ventricular loading conditions at rest (NORM), with compensated mild PAH (PAHComp), with moderately and severely decompensated PAH (PAHDecompMod and PAHDecompSev, respectively), and with additional pacing of the RVfw. Details of the methods used for simulation of ventricular mechanics and hemodynamics under normal and pulmonary hypertensive loading conditions have been published previously.¹⁶

NORM simulation

The NORM simulation represents the human circulation under normal ventricular loading conditions with regular resting values of heart rate (70 bpm), cardiac output (5 l/min), and mean arterial blood pressure (92 mmHg). The heart and large blood vessels were fully compensated by adaptation to mechanical load.¹⁶ The three ventricular walls were activated synchronously.

PAH simulations

The PAHComp simulation represents a state of mild compensated PAH. Mean pulmonary arteriovenous pressure drop was increased from 11 mmHg (1.5 kPa) to 26 mmHg (3.5 kPa), so that mean pulmonary artery pressure (mPAP) increased from 18 mmHg (NORM) to 32 mmHg. Subsequently, size and mass of the heart and large blood vessels were fully compensated by adaptation to normalize mechanical load of the constituting tissues. This adaptation resulted in a 40% increase of RVfw mass. More details of the simulation protocol during adaptation have been published previously.¹⁶ The PAHDecompMod and PAHDecompSev simulations represent a moderate and a severe state of decompensated PAH, respectively. This pathological condition was achieved by further increase of mean pulmonary arteriovenous pressure drop to 49 mmHg (6.5 kPa, PAHDecompMod) and 71 mmHg (9.5 kPa, PAHDecompSev), so that mPAP increased to 55 mmHg and 79 mmHg, respectively. In the PAHDecomp simulations, no further adaptation of ventricular and atrial walls to mechanical load was performed as compared to the PAHComp simulation, thus introducing partial RV decompensation. The three ventricular walls were activated synchronously.

RVfw pacing simulations

To study the acute effect of early RVfw pacing on ventricular mechanics in severely decompensated PAH, the RVfw in the PAHDecompSev simulation was activated

20, 40, and 60 ms earlier than the LVfw and the Sept. No adaptation was applied. Finally, the same pacing protocol was applied to the NORM simulation as control measurement and to the PAHDecompMod simulation to investigate whether the effect of RVfw pacing in PAH depends on degree of decompensation.

Data analysis

In order to test whether the model realistically describes ventricular mechanics in PAH, simulated time courses of circumferential strain in the ventricular walls were compared with clinical strain data obtained in healthy subjects and severe PAH patients by Marcus *et al.*¹⁷ In our simulations, for each ventricular wall, circumferential strain was quantified as the percent change in sarcomere length with respect to reference sarcomere length at moment of aortic valve opening.

For each simulation, LV and RV pressure waveforms were normalized to their maximum values and plotted as function of time. These normalized pressure curves were used to quantify timing difference (Δt_{dec}) between LV and RV pressure decay at half maximum pressure. This timing difference was defined positive when RV pressure decay precedes LV pressure decay.

For each ventricular wall segment, mechanical myofiber load was represented by natural myofiber strain and Cauchy myofiber stress. The area of the obtained myofiber stress-strain loop represents stroke work density, defined as contractile myofiber work per unit of tissue volume (unit: Pa = Joule/m³) per beat.

RESULTS

Below, we first compare simulated and measured circumferential strain patterns under normal healthy and under severe PAH conditions (*Figure 5.1*). Next, we evaluate the effect of compensated and decompensated PAH on cardiac pump function in *Figures 5.2, 5.3, and 5.4*. Finally, we evaluate the effect of RVfw pacing in severely decompensated PAH on cardiac pump function in *Figures 5.5, 5.6, and 5.7*.

NORM and PAH simulations

In the NORM simulation as well as in the healthy subject, time courses of circumferential strain showed synchronous shortening of the ventricular walls during ejection, synchronous lengthening during filling, and similar values of peak circumferential shortening in the three walls (*Figure 5.1, left panels*). Also under severely decompensated PAH conditions, simulated and measured circumferential strain patterns were similar (*Figure 5.1, right panels*), with RVfw

peak shortening being delayed with respect to LVfw and Sept peak shortening and with prolonged RVfw shortening that continues after aortic and pulmonary valve closure. During LV isovolumic relaxation, leftward bulging of the interventricular septum was associated with lengthening of myofibers in the

Figure 5.1. Time courses of circumferential strain in a healthy subject and a pulmonary arterial hypertension (PAH) patient: measurements (*top row*) [Adapted from Marcus *et al.*¹⁷] and simulations (*bottom row*). Both, measurements and simulations show uniform strain curves under normal loading conditions and interventricular mechanical asynchrony with severe PAH, i.e., prolonged duration of RVfw shortening, delayed RVfw peak shortening, and lengthening of the Sept and LVfw during left ventricular isovolumic relaxation. Timing of left ventricular (LV) and right ventricular (RV) filling (FILL), isovolumic contraction (IC), isovolumic relaxation (IR), and ejection (EJ) are indicated in the horizontal bar plots. LVfw, LV free wall; RVfw, RV free wall; and Sept, septal wall.

Sept and LVfw. Maximal leftward septal bulging occurred at moment of RVfw peak shortening. Furthermore, simulated as well as measured RV isovolumic relaxation phase was prolonged and delayed in severe PAH as compared to that in the normal situation (*horizontal bar plots in Figure 5.1*).

In the upper panel row of *Figure 5.2*, time courses of ventricular pressures show that RV pressure increased with PAH. In the PAHDecompSev simulation, RV pressure even exceeded LV pressure during diastole and late systole. The time

Figure 5.2. Time courses of simulated ventricular pressures and circumferential strains under normal (NORM), compensated pulmonary arterial hypertensive (PAHComp), and decompensated pulmonary arterial hypertensive ventricular loading conditions (PAHDecompMod, and PAHDecompSev). Upper panel row: left (LV) and right (RV) ventricular cavity pressures. Middle panel row: normalized LV and RV pressure curves. Lower panel row: circumferential strain in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw). Timing of LV and RV filling (FILL), isovolumic contraction (IC), isovolumic relaxation (IR), and ejection (EJ) are indicated in the horizontal bar plots. Vertical dashed lines indicate moment of aortic valve opening.

courses of normalized LV and RV pressures show that LV and RV pressure rise synchronously in NORM, PAHComp, PAHDecompMod, and PAHDecompSev (*middle panel row of Figure 5.2*). PAH hardly affected timing of LV pressure rise and decay. RV pressure decay, on the other hand, delayed with increase of PAH. RV pressure decay preceded LV pressure decay in NORM and PAHComp, as reflected by positive values of Δt_{dec} , whereas decay of LV pressure preceded that of the RV in decompensated PAH, as reflected by negative values of Δt_{dec} . This delay of RV pressure decay was associated with delayed RV isovolumic relaxation.

In the NORM and PAHComp simulations, time courses of circumferential strains (*lower panel row Figure 5.2*) showed relatively synchronous and uniform strain patterns in the three ventricular walls. In each wall, peak shortening was reached at end-ejection. Peak shortening was 16% in the LVfw as well as in the Sept and 17% in the RVfw. However, with decompensation (PAHDecompMod and PAHDecompSev) circumferential strain patterns changed. During isovolumic contraction, the LVfw and Sept shortened, whereas the RVfw lengthened. Consequently, onset of RVfw shortening was delayed as compared to that of the LVfw and Sept. Peak RVfw shortening was also delayed till moment of mitral valve opening, whereas peak shortening of the LVfw and Sept still occurred at moment of aortic valve closure. The delay of RVfw peak shortening with respect to that of the LVfw was 106 and 136 ms for the PAHDecompMod and PAHDecompSev simulations, respectively. Duration of RVfw shortening increased from 212 ms in the NORM and PAHComp simulations to 294 and 318 ms in the PAHDecompMod and PAHDecompSev simulations, respectively, whereas duration of LVfw and Sept shortening was similar (282 ms) in the NORM and the three PAH simulations.

As shown in *Figure 5.3A*, RV end-diastolic pressure increased from 4 mmHg in the NORM to 15 mmHg in the PAHDecompSev simulation. LV end-diastolic pressure increased less, from 10 mmHg in the NORM and PAHComp simulations to 11 mmHg in PAHDecompMod and 13 mmHg in PAHDecompSev. In the PAHComp simulation, RVfw mass and end-diastolic thickness were increased by 38% and 50%, respectively, whereas LV and RV end-diastolic volumes were not changed with respect to the NORM simulation (*Figure 5.3B*). With decompensation, however, RV end-diastolic volume increased by 54% and LV end-diastolic volume decreased by 9% in PAHDecompSev. As compared to the NORM simulation, LV dP/dt_{max} decreased by 7% in PAHDecompSev (*Figure 5.3C*), while RV dP/dt_{max} increased by 175%.

Figure 5.3. Simulated left (LV) and right (RV) ventricular end-diastolic pressures (**A**), end-diastolic volumes (**B**), maximal rates of pressure rise dP/dt_{max} (**C**), and myofiber work densities (**D**) in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw) under normal (NORM), compensated pulmonary arterial hypertensive (PAHComp), and decompensated pulmonary arterial hyper-tensive ventricular loading conditions (PAHDecompMod and PAHDecompSev).

In the NORM and PAHComp simulations, mechanical load was distributed homogeneously over the ventricular walls as indicated by similarity of myofiber stress-strain relations (*Figure 5.4*). In PAHDecompMod and PAHDecompSev, however, mechanical load was inhomogeneously distributed over the ventricular walls. In the PAHDecompSev simulation, RVfw myofiber work density was increased by 182% with respect to that in the NORM simulation (*Figures 5.3D and 5.4*), whereas Sept and LVfw myofiber work densities were decreased by 27% and 18%, respectively, predominantly due to myofiber lengthening during

LV isovolumic relaxation (*Figure 5.4*). Peak RVfw myofiber stress was three times higher than in the NORM simulation. Furthermore, with decompensation, the RVfw myofiber stress-strain relation was shifted to the right, reflecting increase of mean RVfw sarcomere length from 1.9 μm in the NORM and PAHComp simulations to 2.0 μm and 2.2 μm in the PAHDecompMod and PAHDecompSev simulations, respectively.

Figure 5.4. Simulated myofiber mechanics, in terms of natural myofiber strain and Cauchy myofiber stress, in the ventricular walls under normal (NORM), compensated pulmonary arterial hypertensive (PAHComp), and decompensated pulmonary arterial hypertensive ventricular loading conditions (PAHDecompMod and PAHDecompSev). Zero myofiber strain corresponds to a sarcomere length of 2.0 μm . Moments of aortic valve opening (open dots) and closure (closed dots) are indicated. LVfw, LV free wall; RVfw, RV free wall; and Sept, septal wall.

RVfw pacing simulations

As shown in the upper panel row of *Figure 5.5*, RVfw pacing did not affect the amplitude of ventricular pressures in severe PAH. RV pressure rise and decay occurred earlier with RVfw pacing in PAH, while timing of LV pressure rise and decay did not change (*middle panel row Figure 5.5*). Timing difference Δt_{dec} increased when activating the RVfw earlier than the LVfw and Sept, indicating resynchronization of LV and RV pressure decay. Early RVfw pacing decreased RVfw peak shortening, increased Sept and LVfw peak shortening, resynchronized LV and RV isovolumic relaxation phases, and reduced lengthening of the Sept and LVfw during LV isovolumic relaxation (*lower panel row Figure 5.5*).

Figure 5.5. Time courses of simulated ventricular pressures and circumferential strains in severely decompensated pulmonary arterial hypertension with synchronous activation of the ventricular walls (PAHDecompSev) and with 20-, 40-, and 60-ms RV free wall preexcitation. *Upper panel row:* left (LV) and right (RV) ventricular cavity pressures. *Middle panel row:* normalized LV and RV pressure curves. *Lower panel row:* circumferential strain in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw). Timing of LV and RV filling (FILL), isovolumic contraction (IC), isovolumic relaxation (IR), and ejection (EJ) are indicated in the horizontal bar plots. Vertical dashed lines indicate moment of aortic valve opening.

RVfw pacing decreased RV end-diastolic pressure and volume (Figure 5.6). These parameters reached their minimal value (-7% and -6% as compared to PAHDecompSev, respectively) upon 40-ms RVfw preexcitation. In this latter simulation, LV end-diastolic pressure and volume were not changed. Furthermore, RV dP/dt_{max} was increased (+13%) and LV dP/dt_{max} was decreased (-25%) as compared to the PAHDecompSev simulation.

With early RVfw pacing in severe PAH, RVfw myofiber work density decreased (Figure 5.6D). This decrease of RVfw myofiber work resulted from decrease of peak myofiber stress (up to 8% with 40-ms RVfw preexcitation) and shortening of the RVfw (decrease of myofiber strain) between mitral valve closure and aortic valve opening (Figure 5.7). RVfw pacing also decreased myofiber lengthening in the Sept and LVfw after aortic valve closure, whereas shortening during ejection increased (Figure 5.7). As a consequence, RVfw pacing increased myofiber work density in the Sept and LVfw. Myofiber work was distributed most homogeneously over the ventricular walls upon 40-ms RVfw preexcitation (Figure 5.6D).

Figure 5.6. Simulated left (LV) and right (RV) ventricular end-diastolic pressures (A), end-diastolic volumes (B), maximal rates of pressure rise dP/dt_{max} (C), and myofiber work densities (D) in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw) in severely decompensated pulmonary arterial hypertension with synchronous activation of the ventricular walls (PAHDecompSev) and with 20-, 40-, and 60-ms RVfw preexcitation.

Figure 5.7. Simulated myofiber mechanics, in terms of natural myofiber strain and Cauchy myofiber stress, in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw) in severely decompensated pulmonary arterial hypertension with synchronous ventricular activation (PAHDecompSev) and with 20-, 40-, and 60-ms RVfw preexcitation. Zero myofiber strain corresponds to a sarcomere length of $2.0 \mu\text{m}$. Moments of aortic valve opening (open dots) and closure (closed dots) are indicated.

The model predicted detrimental effects of RVfw preexcitation on ventricular pump function and myofiber mechanics under normal ventricular loading conditions (*NORM simulation*; Figure 5.8): LV and RV end-diastolic pressures increased, LV dP/dt_{max} decreased, and myofiber work density decreased in the RVfw and Sept, whereas it increased in the LVfw.

Figure 5.8. Simulated left (LV) and right (RV) ventricular end-diastolic pressures (A), end-diastolic volumes (B), maximal rates of pressure rise dP/dt_{max} (C), and myofiber work densities (D) in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw) under normal ventricular loading conditions with synchronous activation of the ventricular walls (NORM) and with 20-, 40-, and 60-ms RVfw preexcitation.

Similarly as observed in severely decompensated PAH (Figure 5.6), RVfw preexcitation resulted in redistribution of myofiber work over the ventricular walls in moderately decompensated PAH (PAHDecompMod simulation; Figure 5.9). Under these moderate PAH conditions, myofiber work was distributed most homogeneously over the ventricular walls upon 20-ms RVfw preexcitation. This redistribution, however, was not associated with decrease of end-diastolic ventricular pressures or volumes. These simulation results show that, in our model, the beneficial effect of RVfw pacing on cardiac pump function in decompensated PAH increases with disease severity.

Figure 5.9. Simulated left (LV) and right (RV) ventricular end-diastolic pressures (A), end-diastolic volumes (B), maximal rates of pressure rise dP/dt_{max} (C), and myofiber work densities (D) in the LV free wall (LVfw), septum (Sept), and RV free wall (RVfw) in moderately decompensated pulmonary arterial hypertension with synchronous activation of the ventricular walls (PAHDecompMod) and with 20-, 40-, and 60-ms RVfw preexcitation.

DISCUSSION

In the present study, a mathematical model describing mechanics of ventricular interaction was used to predict the effect of RVfw pacing on ventricular pump mechanics and hemodynamics in severe PAH. With severely decompensated PAH, the model predicted an inhomogeneous distribution of myofiber load over the ventricular walls, expressed by three times higher myofiber work in the RVfw than in the Sept and LVfw. Interestingly, the model predicted that early RVfw pacing decreases the exorbitantly high myofiber work in the RVfw and increases myofiber work in the LVfw and Sept, while global LV and RV pump work remain the same. Apparently, the mechanical interaction of the ventricular walls

allowed local redistribution of myofiber work over the ventricular walls. In our simulations, an optimal moment of RVfw preexcitation was found resulting in homogeneous distribution of myofiber work over the ventricular walls and moderate improvement of RV pump function.

Comparison of measured and simulated ventricular geometry and wall mechanics in compensated and decompensated PAH

Similarly as observed in experimental animals with mild chronic RV pressure overload,^{19,20} the RVfw was hypertrophied in the PAHComp simulation, while resting LV and RV end-diastolic volumes were not changed. Increasing pulmonary resistance without further cardiac load adaptation (PAHDecompMod and PAHDecompSev simulations), however, resulted in RV dilatation, decrease of LV volume, and prolonged as well as delayed RV isovolumic relaxation. All these changes are in agreement with measurements as obtained in patients with severe PAH.^{9,25} The simulated circumferential strain patterns in the three ventricular walls were in close agreement with measurements in healthy subjects and PAH patients.¹⁷ Measurements in and simulations of severe PAH showed prolonged RVfw shortening associated with lengthening of the Sept and LVfw during LV isovolumic relaxation. All these similarities between simulations and measurements show that our model enables realistic simulation of ventricular mechanics under normal as well as pulmonary arterial hypertensive ventricular loading conditions. Despite these qualitative similarities, however, lengthening of the Sept and LVfw during LV isovolumic relaxation appeared underestimated in the PAHDecompSev simulation as compared to the lengthening measured in the specific PAH patient of *Figure 5.1*. Apparently, the interventricular mechanical asynchrony as measured in the specific PAH patient cannot be entirely explained by normal sarcomere physiology as simulated by our sarcomere model.¹⁶ In the pathological PAH situation, the effect of decompensation on local myofiber mechanics may be aggravated. This is in agreement with the fact that in myocardial cells isolated from decompensated failing hearts action potential duration is prolonged as compared to that in normal cells.²⁷

In patients with severe PAH, LV end-diastolic volume is significantly smaller ($\geq 25\%$) than in healthy controls.^{9,17} In our PAHDecompSev simulation, however, we observed a smaller decrease (9%) (*Figure 5.3B*). This discrepancy most likely resulted from the assumption of constant cardiac output for all simulations. This was assumed in order to study the isolated effect of increased pulmonary peripheral resistance on ventricular mechanics and hemodynamics. In a clinical

study comparing healthy controls with severe PAH patients, cardiac output was significantly smaller in PAH patients ($\geq 25\%$).⁹ If we would assume a similar reduction of cardiac output in our simulations, a similar change of LV end-diastolic volume is expected.

Comparison of measured and simulated effects of pacing in decompensated PAH

The beneficial effect of early RVfw pacing in chronically RV overloaded hearts seems to be supported by experimental data published recently by Handoko *et al.*¹⁰ In this study, the effect of RVfw pacing was investigated in a Langendorff set up of hearts isolated from rats with chronic pulmonary hypertension and right heart failure. Similarly as observed in our simulations, with RVfw preexcitation, an optimal pacing setting was found resulting 1) in maximal improvement of RV systolic function (8.5% increase of RV $dP/dt_{\max}$), 2) in decrease of timing difference of LV and RV pressure decay, and 3) in resynchronization of LV and RV peak pressure. Furthermore, in this study, RVfw pacing did not detrimentally affect LV pump function or coronary perfusion. Thus, the results of our simulation study and of the experimental study by Handoko *et al.* mutually support and complement each other.

In an open-chest pig model of acute RV pressure overload and complete AV-block, Quinn *et al.*²² also showed a beneficial effect of RVfw pacing on cardiac performance. In this study, early activation of the RVfw with respect to the LVfw resulted in increase of cardiac output, decrease of LV $dP/dt_{\max}$, and increase of RV $dP/dt_{\max}$. In our simulations, the largest decrease of RV end-diastolic pressure and volume was observed with 40-ms RVfw preexcitation (*Figure 5.6*). Similarly, in the experiments by Quinn *et al.*, maximal increases of cardiac output and RV $dP/dt_{\max}$ occurred when the RVfw was 37 ms earlier activated than the LVfw. Simulations as well as measurements showed that, during this optimal pacing setting, LV and RV pressure waveforms were resynchronized.

The simulations of RVfw pacing in a normal heart (*Figure 5.8*) are in agreement with experimental findings on RV pacing as well as left bundle branch block, indicating the combination of impairment of LV pump function, decrease of Sept and, to a greater extent, of RVfw workload, increase of LVfw workload, and moderate increase of RV pump function (RV $dP/dt_{\max}$).^{13,21}

Potential mechanism behind interventricular mechanical asynchrony in PAH

It is important to realize that in the PAHDecomp simulations all three ventricular walls were activated simultaneously, thus simulating a decompensated PAH condition without conduction delay. The mechanical asynchrony, especially the prolonged RVfw shortening observed in the PAHDecomp simulations, is explained by the basic property of our model¹⁶ that duration of mechanical myofiber activation increases with sarcomere length. This latter property is well known from experiments on isolated cardiac muscle.²⁶ Our simulation results suggest that interventricular mechanical asynchrony in PAH is a direct consequence of stretching the RVfw (RV decompensation). Therefore, it seems safe to assume that the interventricular mechanical asynchrony as reported among patients with severe PAH by Marcus *et al.* also indicates RV decompensation.¹⁷ A spin-off of the present study may therefore be that detection of mechanical interventricular asynchrony could be used as an index of RV decompensation.

Study limitations

Obviously, conditions in a computer simulation may differ considerably from those in patients. In our model, each ventricular wall is lumped into a spherical wall segment containing a single contractile fiber describing representative passive and active sarcomere properties of the entire wall.¹⁶ Although this simplified setup allows inhomogeneity of material properties to some extent, i.e., between ventricular walls, it does not allow local inhomogeneities of material properties within a single wall. In our RVfw pacing simulations, the effect of activation spread away from the pacing site was not included. Mechanical activation time of the RVfw represented representative average activation time. Therefore, with this model we were not able to test the effect of pacing at different locations within the RVfw. Nevertheless, the qualitative and sometimes quantitative agreement between our model simulations and experimental as well as clinical observations indicate that the simplifications made in the simulations may not obscure first-order effects of RVfw pacing on ventricular mechanics and pump function in severe PAH. The present study only focuses on the acute hemodynamic effects of RVfw pacing. Long-term effects are not considered. However, in analogy with cardiac resynchronization in dyssynchronous ventricles, acute hemodynamic effects can be expected to be maintained over time and may even lead to further improvements by reverse remodeling.³

The effect of tricuspid regurgitation, which often exists in severe PAH and which leads to RV volume overload, is not included in the present simulations. RVfw pacing may aggravate tricuspid regurgitation by changing synchrony of RV papillary muscle activation but may also decrease it by reducing RV end-diastolic volume and thereby tricuspid annular dilatation.

Previous experimental studies showed that PAH leading to RV decompensation and heart failure is associated with structural remodeling of the RVfw myocardium (summarized in a review by Bogaard *et al.*⁴). Ischemia and interstitial fibrosis may locally change active and passive myocardial material properties in severe PAH. Although such changes were not included in our simulations of decompensated PAH, we expect minor influence on the decreasing effect of early RVfw pacing on local mechanical work. Whether the translation of work homogenization to improvement of cardiac pump function, as observed in our simulations, is affected by such change of myocardial material properties is unknown. Nonetheless, Handoko *et al.* showed acute improvement of RV pump function with RVfw pacing in remodeled and failing hearts of rats with PAH.¹⁰

Clinical implications

The present study may provide a theoretical framework for a novel therapeutic strategy for severely decompensated PAH patients. Although decrease of pulmonary vascular resistance remains the primary therapeutic target in PAH patients, RVfw pacing as an additional treatment may contribute to clinical improvement of the patient by unloading the RVfw and thereby delaying development of RV failure. Furthermore, it might be useful as bridge to thoracic organ transplantation in these patients. Clearly, more experimental and clinical evidence is needed to prove that the predicted beneficial effect of RVfw pacing is clinically relevant for a PAH patient.

CONCLUSIONS

Our simulations of ventricular mechanics under pulmonary arterial hypertensive conditions show many similarities with data obtained in patients. Both, simulations and measurements show interventricular mechanical asynchrony in severely decompensated PAH, associated with prolonged duration of RVfw shortening and inhomogeneous distribution of myofiber load over the ventricular walls. Early RVfw pacing results in more synchronous LV and RV pressure decay, more homogeneous distribution of myofiber load over the

ventricular walls, and slight improvement of RV pump function. Our simulations suggest that the potential of RVfw pacing as a novel therapeutic approach in PAH patients should be further investigated.

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Chapter 6

Left Ventricular Underfilling and Not Septal Bulging Dominates Abnormal Left Ventricular Hemodynamics in Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with abnormal left ventricular (LV) filling hemodynamics (mitral E/A < 1). Pulmonary thromboendarterectomy (PTE) acutely reduces pulmonary vascular resistance resulting in increase of mitral E/A. Abolishment of leftward septal bulging and increase in right ventricular (RV) systolic output are thought to be responsible for increase of mitral E/A. In this study, we quantified the separate effects of leftward septal bulging and of RV systolic output on LV hemodynamics. In 39 CTEPH patients who underwent PTE, transmitral flow velocities and RV hemodynamic data were obtained pre- and postoperatively. A mathematical model describing mechanics of ventricular interaction was fitted to preoperative average values of cardiac output (CO; 4.4 l/min), mean pulmonary artery pressure (mPAP; 50 mmHg), mitral E/A (0.74), and mean left atrial pressure (mLAP; 9.8 mmHg). Starting from this preoperative reference state with leftward septal bulging, PTE was simulated by changing mPAP and CO to average postoperative values (28 mmHg and 5.7 l/min, respectively). Simulated and postoperatively measured data on E/A (1.27 vs 1.48), mLAP (12.6 vs 11.5 mmHg), and septal curvature (both rightward) were consistent. Simulating exclusive decrease of mPAP, mitral E/A increased 26% due to facilitated passive LV filling at 16% lower mLAP, and septal curvature became rightward. Simulating exclusive increase of CO, mitral E/A increased 53%, mLAP increased 62%, whereas leftward septal bulging persisted. Thus, our simulations suggest that increase of mitral E/A with PTE is for two-third caused by increase of RV systolic output and for one-third by abolishment of leftward septal bulging.

INTRODUCTION

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary vascular resistance (PVR) is chronically increased due to resistive lesions in the pulmonary vascular bed. The chronic increase of right ventricular (RV) afterload in these patients is associated with an abnormal left ventricular (LV) filling pattern,^{7, 12, 27, 31} i.e., peak blood flow velocity of the early passive mitral filling wave (E-velocity) is smaller than that of the atrial contraction-induced late active filling wave (A-velocity). Successful treatment with surgical pulmonary thromboendarterectomy (PTE) leads to acute reduction of PVR associated with decrease of mean pulmonary artery pressure (mPAP) and with increase of cardiac output (CO).^{7, 27} Consequently, PTE results in acute improvement of cardiac pump function.^{14, 31, 43} Furthermore, mitral E-velocity increases so that mitral E/A changes from abnormal value ($E/A < 1$) to normal physiological value ($E/A > 1$).

Generally, two different mechanisms have been hypothesized to be responsible for the acute change of the LV filling pattern in CTEPH patients undergoing PTE. The first mechanism comprises the effect of PTE on LV filling via the pulmonary circulation, i.e., reduction of RV afterload leads to increase of RV systolic output and, thus, to increase of LV preload. The second mechanism comprises the effect directly transmitted by the interventricular septum, i.e., reduction of RV afterload is associated with re-establishment of the normal negative transseptal pressure gradient (LV pressure > RV pressure) and, thus, with abolishment of leftward septal bulging. This acute change of septal geometry is assumed to facilitate LV filling.

In the present study, we aimed to quantify the separate contributions of both mechanisms to the change of LV filling hemodynamics in CTEPH patients undergoing PTE.

MATERIALS AND METHODS

In this study, clinical measurements, as obtained in a group of CTEPH patients undergoing PTE, are combined with a computational modeling approach that allows quantitative discrimination between the effect of increased RV systolic output and of decreased leftward septal bulging on LV filling hemodynamics in these patients.

Patient data

Patient characteristics and a full description of data acquisition have been published previously.²⁷ For the present study, relevant details of the patient population, of the echocardiographic and catheterization measurements, and of the statistical analysis, are summarized below.

Patient population

The patient group consisted of 39 consecutive patients (24 men and 15 women, mean age 55 ± 11 years) with surgically accessible CTEPH who underwent successful PTE. All patients were classified as New York Heart Association class III and IV.

Echocardiography

All patients underwent a standard echocardiographic examination 10 ± 7 days (mean $\pm$ SD) before PTE. Pulsed-wave Doppler imaging of transmitral flow velocities was performed to quantify E and A mitral flow velocities. Heart rate was determined from the electrocardiogram during the Doppler echocardiographic measurements. This echocardiography protocol was repeated 10 ± 6 days after PTE.

Right heart catheterization

All patients underwent right heart catheterization within 48 h of preoperative echocardiography. A 7.5F Swan Ganz catheter was used for invasive measurement of mPAP and mean pulmonary capillary wedge pressure. Cardiac output was obtained by the thermodilution method. Mean arterial blood pressure was measured noninvasively. This catheterization protocol was repeated postoperatively within 72 h of the postoperative echocardiogram.

Statistics

Echocardiographic and hemodynamic patient data are expressed as mean $\pm$ SD and are summarized in *Table 6.1*. A two-tailed Student t-test for paired populations was used to compare pre- and postoperative measurements of echocardiographic and hemodynamic parameters. A *p*-value <0.05 was considered statistically significant.

Table 6.1. Catheterization and echocardiographic data obtained in 39 CTEPH patients before and after PTE.

	Before PTE	After PTE	p-value
Catheterization data			
CO (l/min)	4.4 ± 1.1	5.7 ± 0.9	<0.0001
mPAP (mmHg)	50 ± 11	28 ± 9	<0.0001
PCWP (mmHg)	9.8 ± 5.0	11.5 ± 4.5	0.04
MAP (mmHg)	93 ± 6	95 ± 7	NS
Echocardiographic data			
E (cm/s)	52.5 ± 20.5	82.5 ± 18.5	<0.0001
A (cm/s)	68.0 ± 17.9	60.1 ± 17.1	NS
E/A (-)	0.74 ± 0.22	1.48 ± 0.69	<0.0001
HR (bpm)	80 ± 16	81 ± 15	NS

These patient data have been previously published by Mahmud *et al.*²². NS indicates that the parameter is not significantly different after PTE.

A = peak flow velocity of late mitral filling wave; CO = cardiac output; CTEPH = chronic thromboembolic pulmonary hypertension; E = peak flow velocity of early mitral filling wave; E/A = mitral E/A ratio; HR = heart rate; MAP = mean arterial blood pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PTE = pulmonary thromboendarterectomy.

Computer simulations

Model design

For the present study, the TriSeg model²⁵ of ventricular mechanics was embodied in the CircAdapt model describing mechanics of the whole human circulation.¹

The TriSeg model of ventricular mechanics, previously described in more detail by Lumens *et al.*,^{24, 25} incorporates mechanical interaction of the LV free wall, the RV free wall, and the interventricular septum resulting in realistic coupling characteristics of LV and RV pump mechanics. In short, three thick-walled spherical segments representing the ventricular walls join in a common junction so that they encapsulate the LV and RV cavity. Given LV and RV cavity volume, area and curvature of the LV and RV free wall are calculated while assuming an initial estimate of septal geometry. From wall geometry, representative myofiber strain is calculated for each wall. From myofiber strain,

myofiber stress is determined using constitutive equations describing sarcomere mechanics. The latter empirical model incorporates sarcomere properties as derived from experiments on isolated cardiac muscle,^{5, 42} i.e., velocity of sarcomere shortening increases with passive stretch, strength of activation increases with sarcomere length, and duration of activation increases with sarcomere length. Using myofiber stress and wall geometry, total radial and axial force components of tension acting on the junction are calculated. Then, septal geometry (initially estimated) is adjusted so that equilibrium of tensional force in the junction is satisfied. As a result, geometries of the three ventricular walls are known, together with myofiber stresses, wall tensions, and ventricular cavity volumes and pressures. Summarizing, the TriSeg model relates global LV and RV pump mechanics to local myofiber mechanics in the three ventricular walls. This relation is based on the principle of conservation of energy, meaning that summed ventricular pump work equals summed mechanical work as generated by the myofibers in the ventricular walls.

The CircAdapt model of the whole circulation¹ creates the required physiological environment (circulatory boundary conditions) for the ventricles as represented by the TriSeg model. The CircAdapt model consists of a network of modules representing myocardial walls, valves, large blood vessels, and peripheral resistances. It allows beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics, e.g., volumes and pressures of the ventricular cavities, geometries and myofiber mechanics of the three ventricular walls, and flows through valves. An important feature of the CircAdapt model is that the number of independent parameters is reduced by incorporating adaptation of cardiac and vascular wall size and wall mass to mechanical load so that stresses and strains in the walls of heart and blood vessels are normalized to tissue-specific physiological standard levels.^{1, 25}

Pulmonary peripheral resistance is modeled as a non-linear resistive module representing the pulmonary microcirculation and connecting the compliant pulmonary arterial and venous blood vessel modules.¹ Instantaneous blood flow through the pulmonary resistance ($q_{\text{pulm}}(t)$, with t representing time) is related to the squared instantaneous pulmonary arteriovenous pressure drop ($\Delta p_{\text{pulm}}(t)$, defined as pulmonary artery pressure – pulmonary venous pressure):

$$q_{\text{pulm}}(t) = \left(\frac{\Delta p_{\text{pulm}}(t)}{\Delta p_{\text{pulm,mean}}} \right)^2 \cdot \text{CO} \quad (6.1)$$

where constant parameters $\Delta p_{\text{pulm,mean}}$ and CO represent mean pulmonary arteriovenous pressure drop and cardiac output, respectively. The non-linearity

of this pressure-flow relationship is in agreement with the one measured in the human and canine lung with normal as well as increased pulmonary peripheral resistance due to pulmonary vascular disease.^{13, 15, 45} Both measured and simulated pulmonary pressure-flow relationships show strong non-linearity at low flow. This non-linearity at low flow is mainly caused by recruitment of pulmonary capillaries, i.e., with rising pressure, more capillaries begin to conduct blood, thus lowering overall resistance. At high flow, most pulmonary capillaries are recruited so that overall resistance changes little. The latter change of resistance in the absence of recruitment is a result of vessel distension.

Instantaneous blood flow $q_{\text{sys}}(t)$ through the systemic resistance is directly proportional to the systemic arteriovenous pressure drop Δp_{sys} (aortic pressure – systemic venous pressure):

$$q_{\text{sys}}(t) = \frac{\Delta p_{\text{sys}}(t)}{\Delta p_{\text{sys,mean}}} \cdot \text{CO} \quad (6.2)$$

where $\Delta p_{\text{sys,mean}}$ represents mean systemic arteriovenous pressure drop defined as mean arterial pressure (MAP) minus instantaneous systemic venous pressure.

The combined CircAdapt/TriSeg model was used to simulate cardiovascular mechanics and hemodynamics under normal healthy ventricular loading conditions (Normal simulation) and under chronic thromboembolic pulmonary hypertensive conditions before (CTEPH simulation) and after (POST-PTE simulation) pulmonary thromboendarterectomy. Furthermore, simulations were performed to quantify the effects of either decrease of mPAP (POST-mPAP simulation) or increase of CO (POST-CO simulation) on LV filling hemodynamics in CTEPH.

In each simulation, systemic venous return is set to pre- and postoperatively measured values of CO (Table 6.2), whereas $\Delta p_{\text{pulm,mean}}$ is chosen so that simulated mPAP equals pre- and postoperatively measured values (Table 6.2). In all simulations, MAP and heart rate are set to their preoperatively measured values (93 mmHg and 80 bpm, respectively) because both MAP and heart rate were not significantly different after PTE (Table 6.1).

Normal simulation

The Normal simulation rendered human cardiovascular mechanics and hemodynamics under normal ventricular loading conditions at rest. Size and mass of cardiac walls and large blood vessels were adapted to normalize mechanical load in the tissues. The methods used for simulation of normal ventricular mechanics and hemodynamics have been published in detail

elsewhere.²⁵ In the Normal simulation, CO was set to the average value measured postoperatively in the CTEPH patients (*Tables 6.1 and 6.2*).

Figure 6.1 shows a schematic representation of the simulation protocol as followed to simulate the different patient conditions as described below.

Figure 6.1: Schematic representation of the simulation protocol. Starting from a reference simulation of normal cardiovascular mechanics and hemodynamics (Normal), the model was fitted to average hemodynamic data measured preoperatively in a group of CTEPH patients (CTEPH simulation). Pulmonary thromboendarterectomy (PTE) was simulated by acutely changing mean pulmonary artery pressure (mPAP) and cardiac output (CO) to average postoperative measurements (POST-PTE simulation). The effect of RV afterload on LV filling hemodynamics in CTEPH patients undergoing PTE was quantified by decreasing mPAP to postoperative value, while keeping CO constant (POST-mPAP simulation). Similarly, to quantify the effect of RV systolic output on LV filling, CO was increased from pre- to postoperative value, while keeping mPAP constant (POST-CO simulation). Abbreviations: A = peak blood flow velocity of the late mitral filling wave; E = peak blood flow velocity of the early mitral filling wave; and mLAP = mean left atrial pressure.

CTEPH simulation

Using the Normal simulation as point of departure, the CTEPH simulation was obtained in two steps. First, PVR was increased so that mPAP was equal to 25 mmHg. Up to this level of RV afterload, we assumed the heart and large blood vessels to be able to adapt their wall size and wall mass so that stresses and strains in the walls are normalized to tissue-specific physiological levels. Moreover, this value of mPAP was chosen because pulmonary hypertension is clinically defined as mPAP > 25 mmHg at rest.¹¹ The adaptation led to a 25% increase of the mass of the RV free wall. Second, several model parameters were varied so that simulated sum of mitral E- and A-velocities, mitral E/A, mean left atrial pressure (mLAP), and mPAP matched the average measurements as obtained preoperatively in the patients (*Table 6.1*), i.e.,

- mitral valve area was varied so that the sum of mitral E- and A-velocities was 1.21 m/s;
- passive stiffness of the left atrial myocardium was varied so that mitral E/A was 0.74;
- passive stiffness of the LV myocardium (LV free wall and septum) was varied so that mLAP was 9.8 mmHg; and
- $\Delta p_{\text{pulm,mean}}$ was varied so that mPAP was 50 mmHg.

During the fitting procedure, no further adaptation of cardiac and vascular walls to mechanical load was performed. Similarly as observed in previous studies,^{23, 25} increase of mPAP from 25 to 50 mmHg without adaptation led to RV decompensation, i.e., increase of RV end-diastolic volume and of RV filling pressure (*Table 6.2*). It was assumed that pulmonary capillary wedge pressure was a reasonable accurate surrogate of mLAP in the present patient group.² The resulting CTEPH simulation served as reference state for each of the remaining three simulations, i.e., POST-PTE, POST-mPAP, and POST-CO.

POST-PTE, POST-mPAP, and POST-CO simulations

The POST-PTE simulation, representing the average CTEPH patient after PTE, was obtained by applying two acute interventions (*Figure 6.1*), as derived from the patient data (*Table 6.1*): 1) $\Delta p_{\text{pulm,mean}}$ was decreased so that mPAP decreased from 50 mmHg to 28 mmHg and 2) CO was increased from 4.4 l/min to 5.7 l/min. The POST-mPAP simulation was obtained by decreasing mPAP to postoperative value, while CO was set to preoperative value. Similarly, the POST-CO simulation was obtained by increasing CO to postoperative value, while mPAP was kept constant at preoperative value.

Assessment of LV filling and septal geometry

Starling function curves are obtained by plotting CO, which reflects LV output, as function of mLAP, which approximates LV filling pressure.³⁴ The Starling curve is afterload dependent and characterizes ventricular function and interaction of the ventricle with the distal vascular system. Under the condition of constant LV pressure load, a shift up and to the left of the LV Starling curve generally indicates improved LV function, with greater output for a given filling pressure. In the present study, Starling curves of the left heart were obtained by variation of CO between 3 and 7 l/min with high preoperative mPAP and with low postoperative mPAP, to assess the effect of RV afterload on left heart function as transmitted by the septum.

To assess the effect of PTE on septal geometry, average septal curvature during the early mitral filling wave (C_{sept}) was quantified. This curvature was defined as the reciprocal of radius of curvature and was defined positive for physiological septal bulging towards the RV cavity.

Sensitivity analysis

The CTEPH, the POST-mPAP, and the POST-CO simulations were used to quantify the relative sensitivity (RS) of the dependent parameter DP for changes of the independent parameters mPAP and CO. For example, $RS_{DP, mPAP}$ indicates relative sensitivity of DP for changes of mPAP:

$$RS_{DP, mPAP} = \frac{\log\left(\frac{DP_{\text{POST-mPAP}}}{DP_{\text{CTEPH}}}\right)}{\log\left(\frac{mPAP_{\text{POST-mPAP}}}{mPAP_{\text{CTEPH}}}\right)} \quad (6.3)$$

where the denominator is a constant value of -0.58. Analogously, $RS_{DP, CO}$ indicates relative sensitivity of DP for changes of CO:

$$RS_{DP, CO} = \frac{\log\left(\frac{DP_{\text{POST-CO}}}{DP_{\text{CTEPH}}}\right)}{\log\left(\frac{CO_{\text{POST-CO}}}{CO_{\text{CTEPH}}}\right)} \quad (6.4)$$

where the denominator is a constant value of 0.26. A value of 1, 0, and -1 for RS indicates a proportional, independent, and reciprocal relationship, respectively. Septal curvature can be zero or negative with pulmonary hypertension. Consequently, RS could not be quantified for C_{sept} because only positive real numbers have real-valued logarithms.

RESULTS

Figure 6.2 shows measured as well as simulated LV filling parameters in CTEPH patients before and after PTE. Similarly as measured in patients, the model predicted increase of mitral E-velocity, mitral E/A, mLAP, and little change of mitral A-velocity with PTE in CTEPH patients. Simulation data indicate that the increase of mitral E/A is predominantly caused by increase of CO (Figure 6.2C, blue line) and to a lesser degree by decrease of mPAP (Figure 6.2C, red line). Increase of CO and decrease of mPAP have opposite effects on mLAP (Figure 6.2D). The increase of mLAP with CO (Figure 6.2D, blue line) is much larger than the decrease with mPAP (Figure 6.2D, red line) resulting in a net increase of mLAP with PTE.

Figure 6.2: LV filling parameters in CTEPH patients before and after PTE: measurements and simulations. Squares with error bars represent measurements (mean $\pm$ standard deviation) in CTEPH patients. Circles represent data points derived from the simulations as defined in Figure 6.1. **A:** peak mitral E-velocity. **B:** peak mitral A-velocity. **C:** mitral E/A-ratio. **D:** mean left atrial pressure (mLAP).

Time courses of simulated mitral and aortic blood flow velocities (*Figure 6.3A*) show that PTE predominantly affected the mitral E-wave and hardly affected the A wave. Increase of CO (*Figure 6.3A, blue line*) caused most of the increase of the E-wave, whereas decrease of mPAP (*Figure 6.3A, red line*) caused a relatively small shift of flow from the late A-wave to the early E-wave. Increase of CO as well as decrease of mPAP resulted in earlier opening of the mitral valve. PTE did not affect timing of mitral and aortic valve closure. Consequently, duration of the LV isovolumic relaxation phase decreased from 124 ms (CTEPH) to 90 ms (POST-PTE). Furthermore, PTE resulted in relatively little changes of duration of LV ejection (increase from 234 ms to 244 ms) and of LV isovolumic contraction (decrease from 46 ms to 34 ms). LV Tei (or myocardial performance) index, defined as the sum of LV isovolumic contraction and relaxation time divided by LV ejection time,⁴¹ decreased significantly from 0.73 to 0.51.

Time courses of simulated septal curvature (*Figure 6.3B*) show that the interventricular septum is relatively flat in the CTEPH simulation. After aortic valve closure, septal curvature decreases quickly to negative value at moment of mitral valve opening. This decrease of septal curvature corresponded with a rapid leftward septal motion during the LV isovolumic relaxation phase. As a result, the septum bulges towards the LV cavity during early LV filling. In the POST-PTE simulation, septal curvature was increased to nearly normal values. The increase of septal curvature with PTE resulted almost entirely from decrease of mPAP rather than from increase of CO. The effect of PTE on septal motion is clearly illustrated by supplemental echocardiographic movies showing ventricular geometry in parasternal short axis view as obtained pre- and postoperatively in a CTEPH patient. The first movie (Data supplement: Movie I) demonstrates a flat interventricular septum and rapid end-systolic leftward septal motion in a CTEPH patient before PTE. The second movie (Data supplement: Movie II) demonstrates abolishment of septal flattening and leftward septal motion after PTE. For qualitative comparison with these measurements, two additional movies demonstrate simulated ventricular geometry and time courses of ventricular pressures as obtained from the CTEPH and POST-PTE simulations (Data supplement: Movie III and Movie IV, respectively).

Table 6.2 contains the values of several hemodynamic and geometric parameters in all simulations. These data show that mitral E/A, mitral E-velocity, C_{sept} , LV end-diastolic volume, and LV as well as RV ejection fraction increased from subnormal values in the CTEPH simulation to normal values in the POST-PTE simulation. Similarly, RV end-diastolic volume decreased from a pathologically high value to a normal physiological one. However, mLAP did not decrease to a

Figure 6.3: Simulated time courses of blood flow velocities in the mitral and aortic valves and of septal curvature. See Figure 6.1 for definitions of simulations. **A:** time courses of mitral (positive) and aortic (negative) blood flow velocities. **B:** time courses of septal curvature. Positive curvature denotes rightward septal curvature, whereas negative curvature denotes leftward septal curvature. Zero curvature represents a flat septum. Simulation duration amounts to 1.5 cardiac cycle. Abbreviations as in Figure 6.1.

normal physiological value but increased by 29% from CTEPH to POST-PTE. Moreover, mean right atrial pressure (mRAP) decreased 30%.

Table 6.2 also presents sensitivity analysis data as derived from the POST-mPAP and POST-CO simulations. The POST-mPAP simulation revealed that mitral E-velocity increased less than proportional with decrease of mPAP, whereas the POST-CO simulation revealed that mitral E-velocity increased more than proportional with CO. Furthermore, mitral A-velocity decreased less than proportional with mPAP, whereas it was not affected at all by CO. Summarizing, these data suggest that, in

Table 6.2. Sensitivity analysis quantifying effects of changes in CO and in mPAP on cardiac hemodynamics and geometry with PTE in CTEPH.						
	NORM	CTEPH	POST-PTE	POST-mPAP	POST-CO	
			Δ [%]	Δ [%]	Δ [%]	RS _{CO}
Model parameters						
set to patient data						
CO (l/min)	5.7	4.4	5.7	4.4	5.7	+1
mPAP (mmHg)	17	50	28	28	50	0
Simulated left heart parameters						
E/A (-)	1.24	0.77	1.27	0.97	1.18	+1.64
E (m/s)	0.81	0.52	0.83	0.60	0.81	+1.66
A (m/s)	0.66	0.68	0.65	0.62	0.68	+0.02
mLAP (mmHg)	7.3	9.8	12.6	8.2	15.8	+1.85
LV EF (%)	50	45	50	43	52	+0.57
LV EDV (ml)	142	121	141	126	136	+0.45
C _{sept} (1/m)	25.6	-0.8	19.8	17.9	1.2	-
Simulated right heart parameters						
mRAP (mmHg)	2.5	10.3	7.2	5.1	15.5	+1.56
RV EF (%)	49	30	46	38	36	+0.72
RV EDV (ml)	145	182	152	143	196	+0.29

See Figure 6.1 for definitions of simulations. Grey and black cells indicate parameters set and fitted, respectively, to average preoperative measurements obtained in CTEPH patients undergoing PTE. indicates change in terms of percentage of parameter value with respect to its value in the CTEPH simulation.

C_{sept} = mean septal curvature during early mitral filling wave; EDV = end-diastolic volume; EF = ejection fraction; LV = left ventricular; mLAP = mean left atrial pressure; RV = right ventricular; other abbreviations as in Table 6.1.

CTEPH, mitral E/A is four times more sensitive to relative changes of CO ($RS_{CO} = +1.64$) than to those of mPAP ($RS_{mPAP} = 0.40$). Apparently, the increase of mitral E/A with PTE resulted predominantly from increase of RV systolic output and not so much from normalization of septal geometry.

Figure 6.4 shows LV Starling curves as obtained by variation of CO with high preoperative mPAP (solid line) and with low postoperative mPAP (dashed line), while LV afterload was kept constant. Decrease of mPAP resulted in a shift of the LV Starling curve to the left indicating improvement of LV performance. In the CTEPH patients, however, mLAP increased with PTE (Figure 6.4: from closed to

Figure 6.4: Simulated left heart function curves with high preoperative mPAP (solid line) and with low postoperative mPAP (dashed line). Crosses indicate pre- and postoperative average values and their standard deviations as measured in the CTEPH patients. Data points obtained from the POST-mPAP simulation (open diamond on dashed line) and POST-CO simulation (open diamond on solid line) are indicated. Note that measured pulmonary capillary wedge pressure (PCWP) is assumed to be a reasonable accurate surrogate of mean left atrial pressure (mLAP) in the present patient group. Abbreviations as in Figure 6.1.

open circle). When exclusively increasing CO in our model (POST CO simulation) to average postoperative value (5.7 l/min), mLAP increased 62% (*Figure 6.4: from closed circle to open diamond on solid line*). When changing both mPAP and CO to average postoperative values (*Figure 6.4: from closed circle to open square on dashed line*), mLAP increased 29% to a value close to the actual one measured postoperatively in the patients (*Figure 6.4: open circle*).

DISCUSSION

In the present study, we assessed the effect of PTE on LV filling mechanics and hemodynamics in CTEPH patients by fitting a mathematical model of cardiovascular mechanics and hemodynamics including ventricular interaction to measurements obtained in a group of CTEPH patients before and after PTE. The model was made pathology-specific by fitting it to average preoperative patient data. Starting from this preoperative reference state, PTE was simulated by decreasing mPAP and by increasing CO acutely to average postoperative values. Simulated postoperative LV filling hemodynamics was in agreement with postoperative measurements (*Figure 6.2*). The added value of our modeling approach was that the effect of leftward septal bulging and the effect of CO on LV filling could be separated quantitatively by exclusively decreasing mPAP and by exclusively increasing CO to postoperative values, respectively. The latter model simulations suggested that 1) mitral E/A was about four times more sensitive to relative changes of CO than to those of mPAP, 2) mitral A-velocity was relatively insensitive to acute changes of CO and mPAP, and 3) septal curvature during early LV filling was very sensitive to changes of mPAP and relatively insensitive to changes of CO (*Table 6.2*). These simulation data suggest that increase of mitral E/A with PTE in CTEPH patients is largely the effect of increased RV systolic output and that abolishment of leftward septal bulging is of minor importance.

The acute effect of PTE on LV filling hemodynamics as predicted by our model was qualitatively as well as quantitatively similar to the effect as measured postoperatively in the CTEPH patients (*Figure 6.2*), whose average preoperative data were used as input for our model. Mitral E/A, mitral E-velocity, and mLAP were increased while mitral A-velocity was relatively unaffected after PTE. The simulated effect of PTE on ventricular cavity volumes is also in close agreement with the effect as derived from pre- and postoperative MRI measurements in CTEPH patients undergoing PTE.³⁵ These measurements as well as our simulations show that, under CTEPH conditions before PTE, LV end-

diastolic volume, LV ejection fraction, and RV ejection fraction are significantly decreased whereas RV end-diastolic volume is significantly increased with respect to values simulated and measured under normal physiological conditions. Furthermore, simulated as well as measured ventricular end-diastolic volumes and ejection fractions changed to normal physiological values after PTE.³⁵ In our simulations as well as in patients with CTEPH,³⁰ the favorable effect of successful PTE on global LV performance is reflected by significant decrease of LV Tei index. Also, septal geometry was simulated realistically before and after PTE. Similarly as observed in CTEPH patients,^{16, 35} our simulations showed a major change of septal curvature with PTE (*Figure 6.3B and Table 6.2*), i.e., from negative septal curvature (leftward septal bulging) to physiological positive septal curvature (rightward septal bulging) after aortic valve closure and during early LV filling. Since septal geometry directly depends on the transeptal pressure gradient,⁸ decrease of mPAP rather than increase of CO resulted in abolishment of leftward septal bulging by re-establishment of the normal negative transeptal pressure gradient (LV pressure > RV pressure). Supplemental movies show strong similarity between simulated and measured septal motion before and after PTE in CTEPH (Data supplement: Movies I-IV). All these similarities between simulations and measurements show that our model enables realistic simulation of ventricular mechanics and hemodynamics under pre- and postoperative CTEPH conditions.

The leftward shift of the LV Starling curve with decrease of mPAP (*Figure 6.4*) indicates that the LV fills at lower diastolic pressure. This finding is in agreement with experiments in cardiac preparations in which direct mechanical ventricular interaction via the septum had been preserved but series ventricular interaction via the pulmonary circulation had been abolished.^{9, 32, 40, 44} These studies showed that decrease of RV afterload decreased LV end diastolic pressure as a direct result of geometrical changes such as reduction of leftward septal bulging. LV afterload and filling volume were kept constant during these experiments.

In addition to these experimental data, our POST-mPAP and POST-CO simulations show how a decrease of RV afterload and how an increase of RV systolic output, respectively, affect clinical LV filling parameters as measured in CTEPH patients. In the POST-mPAP simulation, decrease of mPAP was associated with 9% decrease of mitral A-velocity and with 14% increase of mitral E-velocity. Apparently, the acute abolishment of leftward bulging of the interventricular septum facilitates passive LV filling (increase mitral E-wave) and results in redistribution of blood flow from the late to the early mitral filling

phase evidenced by a 26% increase of mitral E/A in the POST-mPAP simulation (*Figures 6.2 and 6.3*). In the POST-CO simulation, however, increase of CO did not affect mitral A-velocity but resulted in 54% increase of mitral E-velocity. In CTEPH patients, PTE resulted in a small (not significant) decrease of mitral A-velocity and in a significant increase of pulmonary capillary wedge pressure (*Table 6.1*).^{12, 27} In combination with these latter observations in patients, our simulations show that decrease of RV afterload and associated abolishment of leftward septal bulging, could only explain a relatively small part (~30%) of the increase of mitral E/A observed in patients undergoing PTE. Increase of CO, however, accounted for most (~70%) of the increase of E/A with PTE.

Our finding that an exclusive 30% increase of CO (POST-CO simulation) did not affect mitral A-velocity and resulted in 54% increase of mitral E-velocity is in agreement with Doppler measurements obtained before and after hemodialysis in patients with renal insufficiency but without overt heart disease.³⁹ In these patients, the decrease of circulating blood volume as a result of hemodialysis is associated with a 13% decrease of CO, whereas heart rate and systemic blood pressures did not change significantly. This decrease of CO was associated with ~30% decrease of mitral E-velocity and mitral E/A, whereas mitral A-velocity remained unchanged. Although pulmonary artery pressure and septal geometry are unknown in this patient group, it is very unlikely that these parameters are significantly different before and after hemodialysis. Therefore, these data strongly support our conclusion derived from our simulations of PTE, i.e., increase of mitral E/A with PTE predominantly results from increase of LV preload rather than from release of LV compression by the septum.

In animal models with chronic RV pressure overload, LV systolic function (contractility) appeared unaffected.^{10, 17, 18, 20} Thus, increase of CO with PTE is most likely the result of improved RV systolic function. This latter improvement may have several causes. First, decrease of RV afterload in decompensated pulmonary hypertension results in reduction of interventricular mechanical dyssynchrony^{23, 26, 28} and, thus, in a more coordinated contraction of the three ventricular walls with less leftward septal bulging. This may, therefore, account for an indirect effect of decreased leftward septal bulging on LV filling hemodynamics via improvement of RV systolic output. Second, in patients with CTEPH, decrease of RV afterload by PTE has been shown to significantly reduce tricuspid regurgitation.³⁶ Third, PTE and the associated decrease of RV end-diastolic volume may result in an acute reduction of total heart volume and, thus, of pericardial constraint. Acute reduction of pericardial constraint has been shown to increase CO in various animal models of pulmonary hypertension.^{3, 4}

Finally (and speculatively), PTE may lead to improvement of RV coronary perfusion. Exorbitantly high RV pressure may increase intramyocardial pressure in the RV free wall and, thus, increase resistance of the RV coronary vasculature more than that of the LV. This may result in relatively reduced myocardial perfusion of the RV. The acute decrease of RV pressure with PTE may result in a decrease of RV coronary vascular resistance (facilitating RV myocardial perfusion) and also cause a decrease in RV mechanical myofiber load. Consequently, RV contractile function and stroke volume can improve.

Many studies have reported strong correlations between septal curvature and LV filling parameters such as E/A and speculated on the potential detrimental effect of leftward septal bulging on LV filling in patients with pulmonary hypertension.^{7, 19, 21, 27, 31, 33, 38} Although not proven, Gurudevan *et al.*¹² suggested that increase of mitral E/A with PTE predominantly resulted from increase of LV preload rather than from release of LV compression by the septum. However, the relative contributions of both mechanisms could not be quantified from the available patient data alone. Our simulations confirm the hypothesis that increase of mitral E/A with PTE in CTEPH patients is largely the effect of increased RV systolic output while abolishment of leftward septal bulging is of minor importance. However, whether normalization of septal geometry and motion also has an indirect effect on LV filling by increasing RV performance and, thus, RV systolic output, remains unknown. This cannot be tested using our model.

Clinical implications

There has been some debate concerning the relative importance of LV underfilling vs. LV compression by septal bulging in the low-output state of advanced pulmonary hypertension.^{12, 29} The etiology of the LV “diastolic dysfunction” often present in CTEPH has also been controversial.^{22, 27, 37} The results of the present study strongly support the concept that perturbations in LV filling pressure, output, and Doppler flow patterns due to CTEPH are primarily caused by RV outflow obstruction and resultant LV underfilling. Although not negligible, the relative contribution of septal geometry and bulging is considerably less. Also, the increases in cardiac output and LV filling explain the marked improvement in LV Doppler diastolic filling pattern after PTE, rather than changes in septal geometry per se.

Study limitations

Obviously, conditions in a computer simulation may differ from those in patients. An important limitation of our model is the fact that heart rate, ventricular stroke volume, and, hence, cardiac output are prescribed independent model parameters. In reality, however, these parameters are mutually dependent and are tightly controlled in order to maintain mean arterial blood pressure. Thus, the exact mechanism by which PTE results in increase of CO can not be studied with the current model. Nevertheless, the quantitative agreement between our postoperative simulation data and postoperative patient data on LV filling hemodynamics (*Figure 6.2*) indicate that the simplifications made in the simulations may not obscure first-order mechanical effects of hemodynamic and mechanical ventricular interaction on LV filling characteristics in CTEPH patients undergoing PTE.

Although the supplemental movies show qualitative agreement between simulated and measured changes of septal motion due to PTE, septal curvature is not quantified in our patients. Nevertheless, in a previous study,²⁵ we have shown that the relation between septal curvature and transeptal pressure difference in our model is similar to the relation measured in a group of healthy volunteers and patients with pulmonary arterial hypertension.⁶

Tricuspid regurgitation, which often exists in patients with CTEPH and which has been shown to be significantly reduced by PTE,³⁶ is not included in our simulations.

CONCLUSIONS

The effect of PTE on LV filling hemodynamics as predicted by our model was surprisingly similar to the effect as observed in patients with CTEPH. Mitral E/A, mitral E-velocity, LV end-diastolic volume, and septal curvature increased from subnormal values in CTEPH before PTE to normal values after PTE, whereas RV end-diastolic volume decreased to normal value. Our model simulations suggest that 1) mitral E/A is about four times more sensitive to relative changes of cardiac output than to those of mean pulmonary artery pressure, 2) mitral A-velocity is relatively insensitive to changes of cardiac output and mean pulmonary artery pressure, and 3) septal curvature is almost solely dependent of mean pulmonary artery pressure and relatively independent of cardiac output. Our simulation data suggest that one-third of the increase of mitral E/A with PTE in CTEPH patients can be explained by the mechanical effect of decrease of RV pressure overload as transmitted by the septum. The remaining two-third increase of mitral E/A can be attributed to increase of RV systolic output.

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DISCLOSURES

We, the authors of this manuscript, state that there are no conflicts of interest to disclose.

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Chapter 7

Patient-Specific Modeling for Assessment of Ventricular Mechanical Asynchrony in Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is associated with prolonged myofiber shortening in the right ventricular (RV) free wall (RVfw) compared to that in the left ventricular (LV) free wall and with early diastolic lengthening of the septum. It is unclear how, in PAH, mechanical overload of the RVfw leads to the observed ventricular mechanical asynchrony. In this study, we hypothesize that delay of mechanical relaxation of the RVfw alone can explain ventricular mechanical asynchrony in PAH. In 21 PAH patients, aortic and pulmonary arterial pressures were obtained by arm-cuff measurements and right heart catheterization, respectively. Ventricular volume and circumferential strain data were obtained by magnetic resonance imaging. A mathematical model of ventricular mechanics and hemodynamics was fitted patient-specifically to available arterial pressure and ventricular volume data. Delay of RVfw peak shortening as predicted by the model (0.120 ± 0.048 s; mean $\pm$ SD) was similar to the measured value (0.112 ± 0.034 s). Early diastolic septal lengthening was systematically underestimated (6.0 ± 3.0 % simulated vs. 10.1 ± 6.0 % measured). In a subgroup of 4 PAH patients with right bundle branch block, agreement between measured and simulated values of early diastolic septal lengthening improved further by imposing delayed onset of RVfw mechanical activation. In conclusion, we developed a patient-specific modeling approach that enables quantitative assessment of ventricular mechanical asynchrony in a heterogeneous group of PAH patients. Patient-specific simulations showed that, in PAH, ventricular mechanical asynchrony is most likely caused by delay of mechanical relaxation of the RVfw either due to prolonged mechanical activation, delayed onset of activation, or both.

INTRODUCTION

In the normal heart, synchronous activation and relaxation of the left ventricular (LV) free wall (LVfw), the interventricular septum (Sept), and the right ventricular (RV) free wall (RVfw) results in relatively uniform deformation of the ventricular walls during the cardiac cycle.^{20,27,29} In patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), however, RV decompensation is associated with ventricular mechanical asynchrony as evidenced by prolonged duration of shortening and delayed peak shortening of the RVfw as compared to that of the LVfw and the ventricular septum.^{23,27} This ventricular mechanical asynchrony is related to disease severity and functional class of the patient.²³ When left untreated, PAH leads to right heart failure and premature death.^{28,34} Several studies showed that morbidity and mortality of PAH patients are determined by the ability of the RV to maintain normal stroke volume and cardiac output.^{8,32} The mechanism by which pulmonary hypertension leads to ventricular mechanical asynchrony and right heart failure is poorly understood.

Several clinical and experimental studies showed that chronic pulmonary hypertension is associated with significant electrophysiological changes in the RVfw myocardium.^{7,15,21,22} In patients with CTEPH, action potential duration is increased and conduction velocity is decreased in the RVfw compared to those in the LVfw.¹⁵ Moreover, myocyte activation and repolarization are completed later in the RVfw than in the LVfw.⁷ In experimental animals¹⁶ as well as in patients¹⁷ with PAH, profound abnormalities have been observed of the electrocardiogram (ECG) indicating decreased action potential duration heterogeneity and discordance of ventricular depolarization and repolarization. Despite all these important experimental and clinical observations, it is still unknown whether electrophysiological remodeling of the RVfw alone can explain the ventricular mechanical asynchrony in PAH and CTEPH.

In the present study, we aimed to elucidate the mechanism that underlies ventricular mechanical asynchrony in PAH and CTEPH. We assessed the hypothesis that ventricular mechanical asynchrony in patients with chronic pulmonary hypertension is caused by delay of mechanical relaxation of the RVfw. To test this hypothesis, we combined clinical measurements, as obtained in a group of PAH patients, with a novel patient-specific modeling approach. In 21 PAH patients, global hemodynamic status was assessed by measurement of left and right ventricular pressure and volume data using right heart catheterization and magnetic resonance (MR) imaging, respectively.²⁷ Ventricular mechanical

asynchrony was assessed by obtaining time courses of circumferential strain in the three ventricular walls by analysis of MR myocardial tagging images.

A numerical model²⁶ describing cardiovascular mechanics and hemodynamics including ventricular interaction was used to simulate the most likely hemodynamic status of each individual patient. In a first patient-specific simulation, the model was fitted to the ventricular volume and pressure data as obtained in each individual patient while assuming normal physiological behavior of the ventricular myocardium. Then, simulated strain patterns in the RVfw and Sept were compared with the measured strain patterns. In a second simulation step, a subgroup of four patients with coexisting right bundle branch block (RBBB) was further evaluated to test whether delayed onset of RVfw mechanical activation can more accurately explain the ventricular mechanical asynchrony as revealed by the ventricular strain patterns measured in those patients.

METHODS

Patient data acquisition

Patient characteristics

Twenty-one patients (5 men and 16 women, mean age 43 ± 14 years) with chronic pulmonary hypertension were included, i.e., 16 idiopathic PAH and 5 CTEPH. The patient group contained patients with New York Heart Association class II ($n=3$), III ($n=17$), and IV ($n=1$). The medical ethical committee of the VU Medical Center approved the measurements used in the present study. More detailed descriptions of patient characteristics and of data acquisition procedures have been published previously.²⁷ Relevant patient data are summarized in *Table 7.1*.

Pressure data

In all patients, pulmonary artery pressure was measured invasively by right heart catheterization. This pressure registration was used to calculate mean, systolic, and diastolic pulmonary artery pressure. Simultaneously, an arm-cuff blood pressure measurement was performed to obtain systolic and diastolic arterial blood pressure. Additionally, a standard 12-lead ECG was recorded. Based on ECG morphology (*Table 7.1*), a subgroup of four patients had an RBBB (3 incomplete and 1 complete).

Ventricular volume data

LV and RV wall volumes and end-diastolic cavity volumes were calculated from a stack of short-axis cine magnetic resonance (MR) images covering both ventricles.

Ventricular strain data

An MR myocardial tagging procedure was applied with Complementary Spatial Modulation of Magnetization to acquire a time series of tagging images in the mid-ventricular short-axis plane.^{40,41} Midwall circumferential strain patterns in the LVfw, the Sept, and the RVfw were obtained by analyzing the MR tagging images with the Harmonic Phase procedure.^{30,40} Temporal resolution amounted to 14 ms. The ECG R-wave was used as reference point with zero strain. Heart rate (HR) was obtained from the same ECG.

For quantitative analysis, the circumferential strain curves were filtered using a second-order Savitsky-Golay smoothing filter with a frame width of 9 data points.³³ Figure 7.1 shows a typical example of filtered LVfw, Sept, and RVfw circumferential strain curves obtained in a PAH patient (Patient 15).

Figure 7.1: Time courses of circumferential strain as measured in the left ventricular free wall (LVfw), septum (Sept), and right ventricular free wall (RVfw) during a cardiac cycle in a pulmonary arterial hypertension (PAH) patient (Patient 15). Time zero corresponds to peak ECG R-wave serving as zero strain reference. Characteristic strains (ϵ): $\epsilon_{LVfw/RVfw/Sept,min}$ = minimum strain in the LVfw/RVfw/Sept; $\Delta \epsilon_{Sept,dias}$ = early diastolic septal lengthening. Characteristic times (t): $t_{LVfw/RVfw/Sept,min}$ = time to minimum strain in the LVfw/RVfw/Sept; $\Delta t_{RL,min}$ = RVfw – LVfw time delay of minimum strain.

Minimum strain ($\epsilon_{\min}$) and time from ECG R-wave to minimum strain ($t_{\min}$) were calculated for the LVfw, the Sept, and the RVfw (*Figure 7.1*). Ventricular mechanical asynchrony was quantified by the delay of the moment of minimum RVfw strain with respect to moment of minimum LVfw strain ($\Delta t_{RL,\min}$ = time to minimum RVfw strain - time to minimum LVfw strain) and by early diastolic septal lengthening ($\Delta \epsilon_{\text{Sept,dias}}$ = Sept strain at moment of minimum RVfw strain - minimum Sept strain).

Patient-specific simulations

Model design

For the present study, we used a numerical model that simulates ventricular mechanics and hemodynamics realistically under normal and pulmonary hypertensive conditions.^{25,26} This model consisted of a module (TriSeg model²⁶) describing ventricular mechanics, including mechanical interaction of the ventricular walls, embodied in the CircAdapt model describing mechanics of the whole human circulation.¹

In the TriSeg model, three thick-walled spherical segments representing the ventricular walls join in a common junction so that they encapsulate the LV and RV cavity. Given LV and RV cavity volume, area and curvature of the LVfw and RVfw are calculated while assuming an initial estimate of Sept geometry. From wall geometry, representative myofiber strain is calculated for each wall. From myofiber strain, myofiber stress is determined using constitutive equations describing sarcomere mechanics. The latter model²⁶ incorporates experimental findings on isolated cardiac muscle,^{9,36} i.e., velocity of sarcomere shortening increases with passive stretch, strength of activation increases with sarcomere length, and duration of activation increases with sarcomere length. Using myofiber stress and wall geometry, total radial and axial force components of tension acting on the junction are calculated. Then, the initially estimated septal geometry is adjusted so that equilibrium of forces is satisfied in the junction. As a result, ventricular cavity volumes and pressures as well as geometries of the three ventricular walls are known, together with their myofiber stress and strain.

The CircAdapt model of the whole circulation¹ provides the required hemodynamic environment for the ventricles as represented by the TriSeg model. The CircAdapt model is composed of modules representing atrial walls, cardiac valves, large blood vessels, and peripheral resistances. Furthermore, the model allows adaptation of size and mass of cardiac walls and large blood vessels to normalize local mechanical load to tissue-specific physiological levels.^{1,26} The combined CircAdapt/TriSeg model allows beat-to-beat simulation of time-dependent volumes

and pressures of the cardiac cavities, geometries and myofiber mechanics of the cardiac walls, and flows through valves.

In the present study, we developed a patient-specific simulation procedure that enables fitting of the model to measurements as obtained in individual PAH patients.

Simulation of the average PAH patient

The model was initialized by simulation of human cardiovascular mechanics and hemodynamics under normal ventricular loading conditions at rest. The methods used to obtain this normal simulation have been published in detail elsewhere.²⁶ Next, pulmonary vascular resistance was increased so that mean pulmonary artery pressure (mPAP) was equal to 25 mmHg. The heart and large blood vessels were fully compensated by adaptation to this level of increased mechanical load. This value of mPAP was chosen because pulmonary hypertension is clinically defined as mPAP > 25 mmHg at rest.¹¹

Figure 7.2: Schematic representation of the patient-specific simulation procedure. Starting from an initial state, a cardiac cycle was simulated with patient-specific settings of heart rate and ventricular wall volumes. Simulated parameter values VAR_{SIM} are derived from the simulation in the same way as their measured equivalents VAR_{PAT} are derived from the strain patterns measured in the patients. Differences between VAR_{PAT} and VAR_{SIM} are used to improve the fit iteratively by adjusting model parameters PAR . If the difference is below a threshold, iteration stops. Finally, simulated and measured values of characteristic RVfw and Sept strain parameters were compared.

Table 7.1 Measured input parameters (VARPAT) obtained in 21 pulmonary arterial hypertension patients[†]

Patient #	HR [bpm]	Wall Volume [ml]		EDV [ml]		BP [mmHg]		PAP [mmHg]			$\epsilon_{LVfw,min}$ [%]	$t_{LVfw,min}$ [ms]	Etiology
		LV	RV	LV	RV	Sys	Dias	Sys	Dias	Mean			
1	78	112	79	101	157	100	50	101	35	62	-14.1	285	IPAH
2	67	130	259	126	554	110	80	71	28	47	-7.0	270	CTEPH*
3	71	82	57	133	175	120	90	84	31	49	-21.2	315	IPAH
4	61	112	65	71	227	110	75	93	34	54	-13.8	298	IPAH
5	81	155	41	82	146	110	50	102	34	61	-14.5	270	IPAH
6	74	103	104	131	209	NA	NA	83	33	51	-14.1	280	CTEPH**
7	86	116	63	135	176	120	70	97	32	57	-17.5	288	IPAH**
8	57	84	43	169	193	115	65	41	15	28	-15.3	358	IPAH
9	88	85	100	65	181	110	80	109	38	64	-11.1	258	IPAH
10	102	83	81	106	219	120	80	77	40	53	-15.1	228	IPAH**
11	105	71	73	75	176	115	72	112	37	70	-13.2	213	IPAH
12	85	112	68	120	139	120	80	64	21	38	-22.8	320	CTEPH
13	103	75	59	76	176	NA	NA	87	38	60	-13.0	298	IPAH
14	75	82	106	92	247	90	70	89	39	58	-10.2	313	IPAH
15	80	112	61	103	146	120	80	88	29	52	-15.4	310	IPAH
16	80	155	153	129	285	122	67	130	57	90	-12.4	285	IPAH
17	57	103	76	82	213	135	80	98	35	56	-14.4	398	IPAH
18	92	87	64	82	202	100	70	92	33	58	-15.8	228	CTEPH
19	70	97	90	101	294	NA	NA	89	34	55	-15.3	258	CTEPH
20	80	85	41	137	169	100	60	49	11	32	-18.4	252	IPAH
21	98	91	74	95	265	105	65	79	34	50	-18.0	275	IPAH
Mean	80	102	84	105	217	112	71	87	33	55	-14.9	286	
SD	14	24	48	28	89	11	11	20	9	13	3.5	43	

For each measurement, mean value and standard deviation (SD) are presented at the bottom of the table.

[†] Data obtained from Marcus *et al.*²⁷

* Patient 2 had a complete right bundle branch block.

**Patients 6, 7, and 10 had an incomplete right bundle branch block.

BP = brachial arterial blood pressure; CTEPH = chronic thromboembolic pulmonary hypertension; Dias = diastolic; EDV = end-diastolic volume; HR = heart rate; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricular; NA = not available; PAP = pulmonary artery pressure; RV = right ventricular; Sys = systolic; $t_{LVfw,min}$ = time to minimum strain; $\epsilon_{LVfw,min}$ = minimum strain in the LV free wall.

Using the resulting simulation as initial state, the average patient was simulated by fitting the model to the average values of the measurements given in *Table 7.1*. Below, the used fitting algorithm is described in steps (*Figure 7.2*).

Step 1: HR and ventricular wall volumes were set to average values measured in the patient group (*Table 7.1*). LVfw and Sept wall volumes were set to 2/3 and 1/3 of total LV wall volume, respectively, which fractions are normal for PAH patients.^{5,10,18,31}

Figure 7.3: Relations between input parameters (VAR) and adjustable model parameters (PAR) as used for patient-specific fitting. Differences between measured and simulated values of ventricular pressure and volume data and of LVfw circumferential strain were used to adjust cardiac output and other model parameters representing mechanical properties of pulmonary and systemic circulations and of ventricular walls. Abbreviations: SBP/DBP = systolic/diastolic aortic blood pressure; sPAP/dPAP/mPAP = systolic/diastolic/mean pulmonary artery pressure; EDV = end-diastolic volume; LV = left ventricular; RV = right ventricular; Other abbreviations and symbols as in Figure 7.1.

Then, in an iterative fitting procedure, a set of heuristically chosen model parameters (VAR in Figures 7.2 and 7.3) was adjusted so that simulated values of a set of variables (VAR in Figures 7.2 and 7.3) were equal to the corresponding average values as measured in the patient group (Table 7.1).

Step 2: A single cardiac cycle was simulated. All variables VAR were derived from the simulated time courses of arterial pressures, ventricular volumes, and LVfw strain.

Step 3: For each variable VAR, a scaling factor was quantified as the ratio of simulated to measured value (VAR_{SIM} / VAR_{PAT}).

Step 4: The scaling factors were used to adjust model parameters PAR (Figure 7.3). Pulmonary arterial pulse pressure (systolic-diastolic pressure difference) was used to adjust pulmonary artery stiffness. Mean pulmonary artery pressure was used to adjust pulmonary vascular resistance. Analogously, aortic pulse pressure and mean aortic pressure were used to adjust aortic stiffness and systemic vascular resistance, respectively. Mean aortic pressure was estimated by the geometric mean of SBP and DBP.⁶ Cardiac output was adjusted so that minimum LVfw strain ($\epsilon_{LVfw,min}$ in Figure 7.1) was equal to its measured value. Durations of mechanical activation of the three ventricular walls were adjusted proportionally so that simulated time to minimum LVfw strain ($t_{LVfw,min}$ in Figure 7.1) was equal to its measured value. RV and LV end-diastolic volumes were used to adjust RVfw reference area and summed LVfw and Sept reference area, respectively. In the model, reference area of a wall is defined as the midwall surface area at reference sarcomere length of 2.0 μm .²⁶

The iterative fitting cycle (Steps 2-4) was repeated until VAR_{SIM} matched VAR_{PAT} with less than 0.5% error. After about 50-100 cycles, a steady state was achieved representing the circulation of the average PAH patient.

Simulation of the specific PAH patient

For each set of patient-specific measurements given in Table 7.1, the above-mentioned fitting procedure was applied using the average PAH patient as initial state (Figure 7.2). Finally, this resulted in 21 patient-specific simulations.

Additional simulation of RBBB and tricuspid regurgitation

To quantify the effect of delay of RVfw relaxation on ventricular strain patterns, a subgroup of four PAH patients (Patient 2, 6, 7, and 10) with coexisting RBBB was further evaluated. Starting from the thus far found patient-specific fits, onset of mechanical activation of the RVfw was delayed with 30 ms and 60 ms

as compared to that of the LVfw and the Sept. Furthermore, there was clinical evidence of significant tricuspid regurgitation (TR) in Patient 2, i.e., RV stroke volume > 2x LV stroke volume. In this patient, the effect of TR on ventricular strain patterns was investigated by setting leakage orifice area to 10% and 20% of tricuspid valve opening area.

Comparison of simulated and measured strains

For each patient-specific simulation, circumferential strains in the three ventricular walls were quantified relative to the status at moment of aortic valve opening. Linear regression and the Bland-Altman method were used to test similarity of six measured and simulated strain and timing variables, i.e., minimum Sept and RVfw strain, time to minimum Sept and RVfw strain, delay of RVfw minimum strain with respect to LVfw minimum strain, and early diastolic septal lengthening (*Figure 7.1*). Analogously, measured strain curves of the subgroup of patients with RBBB were compared with the strain curves obtained from the simulations with and without additional simulation of RBBB.

Sensitivity analysis

A sensitivity analysis (*Appendix 7.A*) was performed to quantify relative sensitivities of VAR_{SIM} to changes in model parameters PAR.

RESULTS

Patient-specific simulations

In *Table 7.2*, group mean values of strain and timing parameters are presented, as derived from the measured strain curves and as obtained from the patient-specific simulations. Patient group heterogeneity appeared quite large as reflected by high standard deviations of the measured pressures, volumes, and strains (*Table 7.1 and 7.2*). Despite the large heterogeneity, patient-specific simulation resulted in steady state solutions in all patients. Furthermore, average values and standard deviations of the differences between measured and simulated parameter values are shown in *Table 7.2*. The small mean differences between measured and simulated timing parameters suggest that the patient-specific simulation procedure did not result in systematic errors in timing of ventricular strains. Differences between measured and simulated strain parameters, however, show that RVfw peak shortening ($\epsilon_{RVfw,min}$) and early diastolic septal lengthening ($\Delta\epsilon_{Sept,dias}$) were systematically underestimated in our simulations. Moreover, the large standard deviations (about 50% of mean value

of measurements) of the differences of $\Delta t_{RL,min}$ and of $\Delta \epsilon_{Sept,dias}$ show that the used patient-specific fitting procedure does not accurately predict ventricular mechanical asynchrony in this patient group.

Figure 7.4: Measured vs. simulated values of characteristic strain and timing parameters as derived from strain measurements and patient-specific simulations in 21 PAH patients. Linear regression line (solid line) and correlation coefficient (R) are shown, as well as the line of identity (dashed line). Abbreviations as in Figure 7.1.

In Figure 7.4, measured values of strain and timing parameters of all patients are plotted as function of their corresponding simulated values. Regression analysis revealed significant correlations ($p < 0.05$) between measured and simulated values for all three strain parameters (*top row of Figure 7.4*) and for time to minimum RVfw strain. Although the absolute value of early diastolic septal lengthening was underestimated, the patient-specific fitting procedure predicted ventricular mechanical asynchrony (positive $\Delta t_{RL,min}$ and $\Delta \epsilon_{Sept,dias}$) in all patients. Full time courses of measured and simulated strains of all patients are shown in *Appendix 7.B*.

Table 7.2 Measured vs. simulated values of strain parameters: simulations with physiological mechanical properties of the myocardial tissue

	Measurements (Meas)	Simulations (Sim)	Difference (Meas – Sim)
	n=21	n=21	n=21
Strain parameters			
$\epsilon_{\text{Sept,min}}$ (%)	-11.5 ± 3.5	-12.0 ± 3.1	0.5 ± 3.0
$\epsilon_{\text{RVfw,min}}$ (%)	-13.4 ± 3.0	-9.9 ± 3.9	-3.5 ± 3.6
$\Delta\epsilon_{\text{Sept,dias}}$ (%)	10.1 ± 6.0	6.0 ± 3.0	4.1 ± 5.4
Timing parameters			
$t_{\text{Sept,min}}$ (s)	0.263 ± 0.046	0.263 ± 0.044	0.000 ± 0.051
$t_{\text{RVfw,min}}$ (s)	0.397 ± 0.046	0.403 ± 0.069	-0.006 ± 0.049
$\Delta t_{\text{RL,min}}$ (s)	0.112 ± 0.034	0.120 ± 0.048	-0.008 ± 0.049

Data are presented as mean value $\pm$ standard deviation.

$t_{\text{RVfw,min}}$ = time to minimum RVfw strain; $t_{\text{Sept,min}}$ = time to minimum Sept strain; $\epsilon_{\text{RVfw,min}}$ = minimum RVfw strain; $\epsilon_{\text{Sept,min}}$ = minimum Sept strain; $\Delta t_{\text{RL,min}}$ = RVfw – LVfw time delay of minimum strain; $\Delta\epsilon_{\text{Sept,dias}}$ = early diastolic septal lengthening.

Additional simulation of RBBB and tricuspid regurgitation

For the PAH patients with RBBB, time courses of measured ventricular strains are compared with those of simulated strains as obtained from the patient-specific simulations with and without added delay of RVfw mechanical activation (*Figure 7.5*). With 30 ms and 60 ms delay of RVfw mechanical activation, early diastolic septal lengthening ($\Delta\epsilon_{\text{Sept,dias}}$) increased by $4.4 \pm 0.7\%$ and $9.5 \pm 1.3\%$, respectively. Delay of minimum RVfw strain ($\Delta t_{\text{RL,min}}$) increased by 11 ± 13 ms and 26 ± 13 ms, respectively. Moreover, the amplitude of RVfw shortening ($\epsilon_{\text{RVfw,min}}$) increased by $2.1 \pm 0.7\%$ and $3.6 \pm 1.2\%$, respectively. In Patients 6, 7, and 10, best fits of simulated RVfw and Sept strain curves were obtained with 60 ms, 30 ms, and 60 ms delay of RVfw activation, respectively. In Patient 2, however, delay of RVfw activation duration alone (*top rows of Figures 7.5 and 7.6*) did not explain the measured high amplitude of RVfw shortening. Simulation of TR alone (*left column of Figure 7.6*), improved the fit of $\epsilon_{\text{RVfw,min}}$ but decreased $\Delta\epsilon_{\text{Sept,dias}}$. However, adding effects of both RBBB and TR to the simulation resulted in improved fits of $\epsilon_{\text{RVfw,min}}$ as well as $\Delta\epsilon_{\text{Sept,dias}}$ (*right lower corner of Figure 7.6*).

Figure 7.5: Time courses of measured (dashed lines) and simulated (solid lines) circumferential strains in the ventricular walls during a cardiac cycle of 4 PAH patients with right bundle branch block (RBBB). Left column: measured strains are compared with strain curves as obtained by regular patient-specific simulation. Middle and right column: patient-specific simulation with additional effect of RBBB. Timing of zero strain references are indicated by vertical dashed lines. For the measurements, this reference corresponds to the ECG R-wave. For the simulations, this reference corresponds to the moment of aortic valve opening.

Figure 7.6: Time courses of measured (dashed lines) and simulated (solid lines) circumferential strains in the ventricular walls during a cardiac cycle of Patient 2 with chronic thromboembolic pulmonary hypertension, right bundle branch block (RBBB) and tricuspid regurgitation (TR). Upper left corner: measured strains are compared with strain curves as obtained by regular patient-specific simulation. From upper left corner to upper right corner: patient-specific simulation with additional effect of RBBB. From upper left corner to lower left corner: patient-specific simulation with additional simulation of TR. From upper left corner to lower right corner: patient-specific simulation with additional simulation of both RBBB and TR. In Patient 2, best overall fit was achieved by additional simulation of both RBBB and TR (lower right corner). Timing of zero strain references are indicated by vertical dashed lines. For the measurements, this reference corresponds to the ECG R-wave. For the simulations, this reference corresponds to the moment of aortic valve opening.

For the subgroup of PAH patients with RBBB, *Figure 7.7* shows the improvement of the patient-specific fits as a result of additional simulation of RBBB (and TR in Patient 2). For all six characteristic strain parameters, all individual data points moved toward the line of identity when simulating

additional RBBB (and TR in Patient 2). Both, mean and standard deviation of the difference decreased considerably for $\epsilon_{RVfw,min}$, $\Delta\epsilon_{Sept,dias}$, $t_{RVfw,min}$, and $\Delta t_{RL,min}$ (Table 7.3). Additional simulation of RBBB and TR did hardly affect absolute value and timing of Sept peak shortening, i.e., $\epsilon_{Sept,min}$ and $t_{Sept,min}$, respectively. No statistical analysis was performed in this subgroup due to the limited number of patients.

Figure 7.7: Measured vs. simulated values of characteristic strain and timing parameters as derived from strain measurements and patient-specific simulations of 4 PAH patients with RBBB. Open circles (○) indicate data points obtained from the regular patient-specific simulations (also shown in Figure 7.4). Closed circles (●) and diamonds (◆) indicate data points obtained from patient-specific simulations with 30 ms and 60 ms delay of RVfw mechanical activation, respectively. Note that for Patient 2, not only delay of RVfw activation but also TR has been imposed by 10% and 20% leak area of the tricuspid valve. Numbers and arrows indicate patient number and direction of change of simulated parameter value, respectively. Dashed line represents line of identity. Abbreviations as in Figures 7.1 and 7.6.

Table 7.3 Differences between measured and simulated values of strain parameters in four patients with PAH and RBBB: effect of additional simulation of RBBB (and TR in Patient 2)

	Difference (Meas – Sim)	Difference (Meas – Sim)	Difference (Meas – Sim)
Additional simulation	No	30ms Delay of RVfw Activation (10% TR in Patient 2)	60ms Delay of RVfw Activation (20% TR in Patient 2)
	n=4	n=4	n=4
Strain parameters			
$\epsilon_{\text{Sept,min}}$ (%)	1.9 ± 2.3	1.5 ± 1.8	1.1 ± 1.6
$\epsilon_{\text{RVfw,min}}$ (%)	-5.9 ± 5.1	-2.9 ± 3.8	-0.5 ± 2.7
$\Delta\epsilon_{\text{Sept,dias}}$ (%)	4.2 ± 3.6	0.5 ± 3.6	-3.9 ± 3.7
Timing parameters			
$t_{\text{Sept,min}}$ (s)	0.012 ± 0.015	0.011 ± 0.016	0.010 ± 0.016
$t_{\text{RVfw,min}}$ (s)	0.021 ± 0.033	0.016 ± 0.022	0.005 ± 0.017
$\Delta t_{\text{RL,min}}$ (s)	0.019 ± 0.035	0.011 ± 0.019	0.001 ± 0.012

Data are presented as mean difference ± standard deviation of the difference.

RBBB = right bundle branch block; TR = tricuspid regurgitation; Other abbreviations as in Table 7.2.

DISCUSSION

We developed a novel patient-specific fitting procedure to assess ventricular mechanics in 21 patients with PAH. In all patients, measured as well as patient-specifically simulated strain patterns showed early diastolic septal lengthening and delayed peak shortening of the RVfw as compared to that of the LVfw. These parameters of ventricular mechanical asynchrony were systematically underestimated in the patient-specific simulations. In a subgroup of four patients with PAH and RBBB, quantitative agreement between measured and simulated values of early diastolic septal lengthening and delay of RVfw peak shortening improved by delaying onset of RVfw mechanical activation. One of the latter four patients also had significant TR. In this patient, simulation of tricuspid valve leakage in addition to RBBB increased RVfw peak shortening and, thereby, further improved agreement between the simulated and the measured strain patterns.

In the present study, it was found that delay of mechanical relaxation of the RVfw alone predominantly caused ventricular mechanical asynchrony in the ventricular walls of PAH patients. Moreover, it has been shown that this

happened irrespective whether the delay of RVfw relaxation is caused by prolonged RVfw mechanical activation, delayed onset of RVfw activation, or both. This is in agreement with measurements obtained by Hardziyenka *et al.* among CTEPH patients.¹⁵ In these patients, ventricular mechanical asynchrony was related to significant action potential prolongation and conduction slowing in the RVfw as compared to the LVfw. In a subgroup of CTEPH patients with RBBB, they found more pronounced delay of RVfw mechanical relaxation. Other studies showed that the ventricular mechanical asynchrony as a result of delayed mechanical RVfw relaxation may be a target for therapeutic intervention.^{14,25} These studies showed that early pacing of the RVfw may acutely reduce ventricular mechanical asynchrony and, thereby, improve RV pump function.

In all patients, patient-specific fitting resulted in delay of RVfw minimum strain with respect to LVfw minimum strain ($\Delta t_{RL,min}$ in *Figure 7.4*). Mean difference between measured and simulated $\Delta t_{RL,min}$ was close to zero (*Table 7.2*), but the standard deviation of the difference was large. This large standard deviation may be explained by the heterogeneity of the patient group used in this study. Many PAH patients are likely to have considerable TR,^{2,37} RBBB,^{7,12,15} or both. As shown in *Figure 7.6*, simulated $\Delta t_{RL,min}$ decreased with additional simulation of TR, whereas it increased with RBBB. Coexisting TR and RBBB may also explain the systematic underestimation of RVfw peak shortening ($\epsilon_{RVfw,min}$ in *Figure 7.4* and *Table 7.2*) in the simulations without RBBB and TR. As shown in *Figure 7.6*, simulated $\epsilon_{RVfw,min}$ decreased with additional simulation of both TR and RBBB. Unfortunately, the amount of TR was not known for the patient group in this study except for Patient 2. Thus, part of the discrepancy between measured and simulated values of $\epsilon_{RVfw,min}$ (*Table 7.2*) may be caused by neglecting TR in most of the patient-specific simulations.

In patients with severe PAH, early diastolic lengthening of the septum corresponds to leftward septal bulging during LV isovolumic relaxation.^{12,19,26,27,35} In our regular patient-specific simulations, early diastolic septal lengthening ($\Delta \epsilon_{Sept,dias}$) was systematically underestimated (*Figure 7.4* and *Table 7.2*). Interestingly, the degree of underestimation correlated well with $\Delta \epsilon_{Sept,dias}$ as measured in the patients. As shown in *Figure 7.5*, *7.6*, and *7.7*, $\Delta \epsilon_{Sept,dias}$ increased considerably with delay of RVfw mechanical relaxation in the patients with RBBB. Notably, the amount of delay, which was needed to fit $\Delta \epsilon_{Sept,dias}$, increased with measured $\Delta \epsilon_{Sept,dias}$. The latter phenomenon has also been observed in CTEPH patients with and without additional RBBB.¹⁵ It needs further investigation whether the amount of underestimation of $\Delta \epsilon_{Sept,dias}$ by our patient-specific simulation procedure is an indicator of myocardial pathology in the RVfw.

In our simulations of PAH, prolonged mechanical activation of the myofibers in the dilated RV free wall is explained by the normal physiological property of the cardiac muscle that duration of mechanical myofiber activation increases with sarcomere length. This latter property is well known from experiments on isolated cardiac muscle³⁶ and is as such implemented in the constitutive equations describing sarcomere mechanics in the TriSeg model.²⁶ The systematic underestimation of ventricular mechanical asynchrony in our patient-specific simulations suggests that the abovementioned normal physiological behavior of the cardiac muscle is not sufficient to explain the ventricular mechanical asynchrony as measured in patients with severe PAH. Previous experimental studies showed that severe PAH is associated with structural and electrophysiological remodeling of the RVfw myocardium.^{4,15} Ischemia^{13,38,39} and interstitial fibrosis^{3,15,24} in the RV free wall may locally change active and passive myocardial material properties in severe PAH. The disregarding of these pathophysiological aspects in the simulations of severe PAH may partially explain the discrepancy between simulated and measured ventricular mechanical asynchrony.

Besides giving insight in the potential mechanism behind ventricular mechanical asynchrony in PAH patients, the present study also presented a proof of principle showing that the model is feasible for patient-specific simulation of ventricular mechanics in a heterogeneous group of PAH patients. Especially in the subgroup of patients for which additional information about TR and RBBB was used, realistic simulations of local ventricular strain patterns were obtained by fitting the model to a limited number of measured variables. Except for pulmonary artery pressure, all variables were measured non-invasively.

Timing of zero reference strain was defined differently for the measured and the simulated strains. For the simulations, circumferential strain was referred to the status at the moment of aortic valve opening. For the measurements, strain was referred to the circumferential length of the ventricular wall in the first MR tagging image after the ECG R-wave as measured by the MR imaging system. Furthermore, the delay between the true ECG QRS complex and the QRS complex as used by the MR imaging system to trigger image acquisition was unknown. Consequently, measured and simulated strain curves may not be perfectly synchronized. Although this was expected to cause small (<10%) systematic differences between measured and simulated values of minimum strain and time to minimum strain in the ventricular walls, it did not affect delay of RVfw minimum strain ($\Delta t_{RL,min}$ in *Figure 7.1*) and early diastolic septal lengthening ($\Delta \epsilon_{Sept,dias}$ in *Figure 7.1*). Convergence of the patient-specific fit to steady state was not fast (50-100

cardiac cycles) and oscillations occurred due to cross-relationships between most adjustable model parameters (PAR in *Figure 7.3*). Although cross-relations appeared weak (*Appendix 7.A*), quantitative incorporation of these cross-relations in the fitting procedure can possibly accelerate convergence to steady state. However, computational optimization of the fitting procedure was beyond the scope of the present study.

CONCLUSIONS

A novel patient-specific fitting procedure has been used to assess ventricular mechanics in a group of patients with PAH. In all patients, patient-specific simulation predicted ventricular mechanical asynchrony as evidenced by delay of RVfw peak shortening and by early diastolic lengthening of the septum. Comparison of measured and simulated ventricular strain patterns revealed a systematic underestimation of early diastolic lengthening of the septum in the simulations. This underestimation suggests that the asynchrony can only partly be explained on the basis of physiological mechanical properties of the myocardial tissue. In a subgroup of PAH patients with RBBB, agreement between measured and simulated ventricular mechanical asynchrony was further improved by additional delay of onset of RVfw mechanical activation. These findings confirm our hypothesis that, in PAH, ventricular mechanical asynchrony is most likely caused by delay of mechanical relaxation of the RVfw. It has been shown that the asynchrony happened irrespective whether the delay of RVfw relaxation is caused by prolonged RVfw mechanical activation, delayed onset of RVfw activation, or both.

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APPENDIX 7.A: SENSITIVITY ANALYSIS

The simulation of the average PAH patient was used as reference simulation for sensitivity analysis. Starting from this reference, one measured variable VAR_{PAT} (Table 7.1) at a time was varied by 10%. For each variation, a simulation was performed with the fitting procedure (Steps 2-4 in the “Methods” section) until steady state was reached. Each of these simulations was used to quantify the relative sensitivities of the model parameters PAR to a change of the measured variable VAR_{PAT} . Relative sensitivity (RS) was defined as:

$$RS = \frac{\log(\Delta PAR)}{\log(\Delta VAR_{PAT})} \quad (7.A1)$$

A value of 1, 0, and -1 for RS indicates a proportional, independent, and reciprocal relationship, respectively.

Table 7.A Relative sensitivities of simulated input parameters VAR_{SIM} to changes of model parameters PAR

PAR →	k_{AO} [-]	p_{AO} [kPa]	k_{PA} [-]	$p_{DropPulm}$ [kPa]	$A_{ref,LV}$ [cm ²]	$A_{ref,RVfw}$ [cm ²]	CO [ml/s]	t_{Act} [s]
Reference value	10.1	12.2	19.1	6.9	114	154	67	0.619
$VAR_{SIM} \downarrow$								
SBP	2.1	0.6	0.1	-0.1	-0.3	0.0	0.0	-0.4
DBP	-1.9	0.4	0.0	0.0	0.0	0.0	0.0	0.2
sPAP	0.0	0.0	2.8	0.2	0.0	-0.1	0.0	0.0
dPAP	0.0	0.0	-1.0	-0.1	0.0	0.0	0.0	0.0
mPAP	0.0	0.0	-1.3	1.0	0.0	-0.2	0.0	0.0
LV EDV	0.1	0.0	0.6	0.0	0.4	-0.2	0.7	-0.3
RV EDV	0.0	0.0	0.0	0.0	0.0	0.5	0.1	0.0
$\epsilon_{LVfw,min}$	0.0	0.0	0.6	-0.1	-0.2	-0.1	0.8	0.0
$t_{LVfw,min}$	-0.4	0.1	0.0	0.0	0.1	0.1	0.0	0.9

The absolute reference values of the variable model parameters PAR are derived from the average PAH patient simulation. Grey cells indicate relative sensitivities of the VAR_{SIM} - PAR couples as used in the fitting procedure.

Definitions of PAR symbols: $A_{ref,LV/RVfw}$ = reference area LV wall/RV free wall, LV wall includes LV free wall and septal wall; CO = cardiac output; $k_{AO/PA}$ = aortic/pulmonary artery stiffness; p_{AO} = mean aortic pressure; $p_{DropPulm}$ = mean pulmonary arteriovenous pressure drop; t_{Act} = ventricular mechanical activation duration. Definitions of VAR_{SIM} symbols: DBP/SBP = diastolic/systolic aortic blood pressure; dPAP/sPAP/mPAP = diastolic/systolic/mean pulmonary artery pressure; EDV = end-diastolic volume; LV = left ventricular; RV = right ventricular; $t_{LVfw,min}$ = time to minimum strain LV free wall; $\epsilon_{LVfw,min}$ = minimum strain LV free wall.

APPENDIX 7.B: MEASURED VS. SIMULATED PATIENT-SPECIFIC VENTRICULAR STRAIN CURVES

This Appendix presents time courses of measured and simulated circumferential strains of the LVfw, Sept, and RVfw for each individual patient.

Figure 7.B2: Strain data of patients 5-8. Abbreviations and legend details similar as *Figure 7.B1*.

Figure 7.B3: Strain data of patients 9-12. Abbreviations and legend details similar as *Figure 7.B1*.

Figure 7.B4: Strain data of patients 13-16. Abbreviations and legend details similar as *Figure 7.B1*.

Figure 7.B5: Strain data of patients 17-21. Abbreviations and legend details similar as *Figure 7.B1*.

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Chapter 8

General Discussion

INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined as a group of diseases with a common characteristic histopathological pattern of pulmonary vascular remodeling. This vascular remodeling results in resistive lesions in the pulmonary vascular bed progressively leading to chronic elevation of pulmonary arterial pressure.³¹ Eventually, right ventricular (RV) pressure overload due to PAH leads to impairment of cardiac pump function and premature death.

In this thesis, we aimed to elucidate the mechanisms by which pulmonary arterial hypertension (PAH) affects cardiac pump function. For that purpose, we developed a mathematical model of cardiovascular mechanics incorporating hemodynamic and mechanical ventricular interaction (**chapters 3 and 4**). It has been shown that the model enables realistic beat-to-beat simulation of global ventricular pump mechanics, dynamics of septal geometry, and myofiber mechanics in the three ventricular walls under normal as well as pulmonary hypertensive loading conditions (**chapter 4**). In severe PAH, the model predicted similar ventricular mechanical asynchrony as measured in patients. Peak shortening of the right ventricular (RV) free wall was delayed compared to that of the left ventricular (LV) free wall. The interventricular septum lengthened rapidly during the LV isovolumic relaxation phase. We tested pacing of the RV free wall for its potential to treat RV failure in patients with severe PAH (**chapter 5**). These model simulations suggested that early pacing of the RV free wall reduces ventricular mechanical asynchrony and, thereby, improves RV pump function. Furthermore, the model was used to simulate ventricular mechanics in patients with chronic thromboembolic pulmonary hypertension before and after pulmonary thromboendarterectomy (**chapter 6**). Pathology-specific simulations predicted similar improvement of LV filling hemodynamics (increase of mitral E/A-ratio) after pulmonary thromboendarterectomy as measured in a group of patients. It has also been shown that the increase of mitral E/A-ratio with pulmonary thromboendarterectomy is predominantly caused by increase of RV systolic output (hemodynamic ventricular interaction) and to a lesser degree by abolishment of leftward septal bulging (mechanical ventricular interaction). Finally, a patient-specific simulation procedure was designed for assessment of ventricular mechanics and hemodynamics in the individual PAH patient (**chapter 7**). With patient-specific simulation in a group of PAH patients with and without right bundle branch block, it is shown that ventricular mechanical asynchrony is most likely caused by delay of mechanical relaxation of the RV free wall either due to prolonged mechanical activation of the RV free wall, delayed onset of mechanical activation, or both.

In this concluding chapter, we will put the findings as presented in the previous chapters in a broader perspective. We will also focus on study limitations, potential clinical implications, and future studies as derived from our study results.

MODELING MECHANICAL VENTRICULAR INTERACTION USING THE TriSeg MODEL

In the human heart, direct anatomical coupling of the ventricular walls results in mechanical ventricular interaction. Consequently, a change in loading condition of either ventricle directly influences pump function of the other ventricle mediated, among others, by the interventricular septum.^{3, 26, 76, 85, 98} Experimental as well as clinical studies showed that septal geometry and motion are directly related to septal transmural pressure difference.^{21, 26, 46, 56, 79} Septal geometry and motion appeared to be of diagnostic and predictive significance in patients with asynchronous activation of the ventricular walls^{34, 56, 77} and with PAH.^{21, 41, 45, 80}

We developed the mathematical TriSeg model for the assessment of LV and RV mechanics and hemodynamics under normal and pathological ventricular loading conditions (**chapter 3 and 4**). Three ventricular wall segments representing the LV free wall, the septum, and the RV free wall are mechanically coupled on the basis of tensile force equilibrium in their junction. Global LV and RV pump mechanics are related to representative myofiber mechanics in the three ventricular walls, satisfying the principle of conservation of energy. The TriSeg model is embodied as a ventricular module in the lumped CircAdapt model describing mechanics and hemodynamics of the whole human circulation.² The latter model provides the required hemodynamic environment for the ventricles as represented by the TriSeg model, i.e., atrial walls, cardiac valves, large blood vessels, and peripheral resistances. The combined CircAdapt/TriSeg model allows beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics such as volumes and pressures of the cardiac cavities, geometries and myofiber mechanics of the cardiac walls, and flows through the valves. Furthermore, the model allows adaptation of size and mass of cardiac walls and large blood vessels to normalize local mechanical load to tissue-specific physiological levels.^{2, 64}

In a first trial (**chapter 3**), the model was used to simulate ventricular mechanics in the canine heart with synchronous mechanical activation of the three ventricular walls and with asynchronous mechanical activation due to left bundle branch block (LBBB). The simulated results of ventricular mechanics and hemodynamics under normal and LBBB conditions were compared with experimental data obtained before and after acute induction of LBBB in dogs,

respectively. Similarly as observed in dogs with LBBB,^{57, 78, 95} the model predicted 1) delay of pressure rise and decay in the LV as compared to those in the RV, 2) increase of asymmetry of the RV pressure curve, 3) early systolic leftward motion of the septum, and 4) increase of myofiber stroke work in the late activated LV free wall. The surprisingly good agreement between simulations and measurements suggested that the TriSeg model allows realistic simulation of ventricular mechanics including mechanical ventricular interaction and, thereby, extends the application range of the CircAdapt model.

We also simulated ventricular mechanics and hemodynamics in the human heart with normal and increased pulmonary vascular resistance (**chapter 4**). With normal pulmonary vascular resistance, the model predicted realistic ventricular geometry as obtained by adaptation of ventricular wall masses and sizes so that mechanical myofiber stress and strain were normalized to known physiological levels. LV and RV end-diastolic cavity volume were about equal,⁸⁴ whereas the LV free wall and the septum were about 3 times thicker than the RV free wall.^{24, 36, 87} Also LV and RV pressure-volume loops and time courses of blood flow velocities through the cardiac valves were in agreement with measurements obtained in healthy humans and experimental animals.^{30, 39, 47, 83, 91, 92} With increase of pulmonary vascular resistance including load adaptation of the ventricular walls, model simulations showed similar changes of ventricular wall thicknesses, septal geometry, and blood flow patterns through RV valves as observed in patients and experimental animals with PAH. RV free wall thickness increased, whereas thickness of the LV free wall and septal wall hardly changed.⁷⁵ Septal curvature decreased linearly with pressure difference across the septum.^{14, 21, 25, 26, 45, 46, 80} Acceleration time of pulmonary flow velocity (time to peak flow velocity) decreased linearly with increase of mean pulmonary artery pressure.^{13, 20} Furthermore, RV isovolumic contraction and relaxation times increased while pulmonary ejection time decreased.^{91, 99} When increasing pulmonary vascular resistance without load adaptation of the myocardial tissue, the model predicted similar changes of ventricular mechanics and geometry as often associated with RV failure in patients with severe PAH,^{17, 40, 69} i.e., RV dilatation and rapid leftward septal motion following LV ejection.

Based on all these similarities between measurements and simulations (**chapter 3 and 4**), it is concluded that the model is a valuable simulation tool for assessment of time-dependent ventricular mechanics and hemodynamics in patients with PAH. Moreover, the model is applicable in a wide range of disease severity due to its possibility to apply adaptation of the myocardial tissue to mechanical load.

RIGHT VENTRICULAR FREE WALL PACING IN PULMONARY ARTERIAL HYPERTENSION: TREATMENT OF RIGHT VENTRICULAR FAILURE?

In PAH, peak shortening of the RV free wall is delayed as compared to that of the LV free wall and septum. This ventricular mechanical asynchrony appears related to leftward septal bulging, stroke volume, RV free wall stress, disease severity, and functional class of the patient.^{58, 69} As a potential treatment, RV resynchronization therapy has been suggested to improve ventricular mechanical synchrony and, thereby, RV pump function in PAH.^{7, 42, 58, 69}

In **chapter 5**, the TriSeg model is used to predict the effect of early RV free wall pacing on ventricular pump mechanics and hemodynamics in PAH. Severe PAH was simulated by increasing RV pressure load without adaptation (decompensation). This simulation showed many similarities with data obtained in patients with severe PAH, i.e., RV dilatation, delayed peak shortening of the RV free wall as compared to that of the LV free wall and septum, and leftward septal bulging. Furthermore, the model predicted an inhomogeneous distribution of mechanical myofiber load over the ventricular walls. Myofiber work in the RV free wall was three times higher than that in the septum and the LV free wall. Interestingly, preexcitation of the RV free wall by pacing decreased the exorbitantly high myofiber work in the RV free wall and increased myofiber work in the LV free wall and septum. Apparently, the mechanical interaction of the ventricular walls allowed redistribution of myofiber work over the ventricular walls. An optimal time of RV free wall preexcitation was found resulting in most homogeneous distribution of mechanical load over the ventricular walls, best synchrony of RV and LV pressure curves, and moderate improvement of RV pump function, as evidenced by increase of RV dP/dt_{max} , decrease of RV end-diastolic pressure, and decrease of RV end-diastolic volume. These simulations suggested that early pacing of the RV free wall is a potential treatment of RV failure in patients with severe PAH.

The beneficial effect of early RV free wall pacing on RV pump function in PAH is supported by experimental data obtained by Handoko *et al.*³⁷ in isolated hearts of rats with PAH and RV failure. Similarly as observed in our simulations, an optimal pacing setting with RV free wall preexcitation was found resulting in maximal improvement of RV systolic function (8.5% increase of RV dP/dt_{max}) and resynchronization of LV and RV pressure curves. Furthermore, in the study by Handoko *et al.*,³⁷ RV free wall pacing did not detrimentally affect LV pump function or coronary perfusion. Thus, the results of our simulation study in **chapter 5** and of the experimental study by Handoko *et al.*³⁷ mutually support and complement each other.

In our model, each ventricular wall is lumped into a spherical wall segment containing a single contractile fiber describing representative passive and active sarcomere properties of the entire wall.⁶⁴ Despite this simplified representation of the ventricular walls, the qualitative and quantitative agreement between our simulations and experimental as well as clinical observations indicate that the simplifications made in the simulations may not obscure first-order effects of RV free wall pacing on ventricular mechanics and pump function in severe PAH. The study in **chapter 5** only focuses on the acute hemodynamic effects of pacing. Long-term effects are not considered. However, in analogy with cardiac resynchronization in dyssynchronous ventricles, acute hemodynamic effects can be expected to be maintained over time and may even lead to further improvements by reverse remodeling.¹¹

ABNORMAL LEFT VENTRICULAR FILLING HEMODYNAMICS IN PULMONARY ARTERIAL HYPERTENSION: A RESULT OF UNDERFILLING OR COMPRESSION BY SEPTAL BULGING?

In patients with PAH, chronic RV pressure overload is associated with reduced LV end-diastolic volume and abnormal LV filling pattern,^{22, 32, 35, 59, 67, 70, 72, 96} i.e., peak blood flow velocity of the early passive mitral filling wave (E-velocity) is smaller than that of the atrial contraction-induced late active filling wave (A-velocity). This phenomenon might be due to leftward septal bulging, which is believed to hinder passive filling by compressing the LV (mechanical ventricular interaction). Alternatively, the inability of the RV to maintain normal stroke volume is believed to reduce preload of the LV (hemodynamic ventricular interaction). It is still unclear to what extent both mechanisms contribute to impairment of LV filling in PAH patients. In **chapter 6**, the separate contributions of both mechanisms are quantified in patients with chronic thromboembolic pulmonary hypertension (CTEPH) to obtain better understanding of the mechanism by which PAH affects LV filling.

In a group of CTEPH patients, transmitral blood flow velocities and RV hemodynamic data were obtained before and after pulmonary thromboendarterectomy (PTE). The TriSeg model was fitted to preoperative average values of cardiac output (CO), mean pulmonary artery pressure (mPAP), mitral E/A-ratio, and mean left atrial pressure (mLAP). Starting from this preoperative reference state with leftward septal bulging, PTE was simulated by changing mPAP and CO to average postoperative values. The effect of PTE on LV filling hemodynamics as predicted by our model was surprisingly similar to the effect

as observed in patients with CTEPH. Mitral E/A-ratio, mitral E-velocity, LV end-diastolic volume, and septal curvature increased from subnormal values in CTEPH before PTE to normal values after PTE, whereas RV end-diastolic volume decreased to normal value. With our pathology-specific modeling approach, effects of RV pressure overload and of RV systolic output on LV filling hemodynamics could be discriminated quantitatively by simulating either an exclusive decrease of mPAP or an exclusive increase of CO, respectively. With exclusive decrease of mPAP, mitral E/A-ratio increased 26%, mLAP decreased 16%, and leftward septal bulging was abolished. With exclusive increase of CO, mitral E/A-ratio increased 53%, mLAP increased 62%, whereas leftward septal bulging persisted. These data show that increase of mitral E/A-ratio with PTE in CTEPH patients is largely the effect of increased RV systolic output. Abolishment of leftward septal bulging appears to be of less importance.

In patients with chronic RV pressure overload, cardiac output may be decreased due to many functional and morphological alterations of both the RV and the LV. As has been shown for PTE,^{22, 23, 35, 67, 71, 72} lung transplantation,¹⁶ and repair of congenital heart disease,^{65, 66} LV hemodynamic and morphological changes as a result of RV pressure overload remain largely reversible, even after years of illness. The acute reversibility of LV filling hemodynamics after PTE strongly suggests a functional rather than a structural change of the LV myocardium with RV pressure overload due to CTEPH. This concept is confirmed by the simulations of decompensated PAH in **chapters 4 and 5** showing that RV pressure overload mostly increases mechanical myofiber load in the RV free wall, whereas it hardly affects the myofiber stress-strain relation in the LV free wall and the interventricular septum.

In animal models with chronic RV pressure overload, LV systolic function (contractility) appeared unaffected.^{27, 50, 51, 54} Thus, increase of CO with PTE is most likely the result of improved RV systolic performance. This latter improvement may have several causes. First, decrease of RV afterload in decompensated pulmonary hypertension results in reduction of interventricular mechanical dyssynchrony^{61, 66, 69} and, thus, in a more coordinated contraction of the three ventricular walls with less leftward septal bulging. This may, therefore, account for an indirect effect of decreased leftward septal bulging on LV filling hemodynamics via improvement of RV systolic output. Second, in patients with CTEPH, decrease of RV afterload by PTE has been shown to significantly reduce tricuspid regurgitation.⁸¹ Third, PTE and the associated decrease of RV end-diastolic volume may result in an acute reduction of total heart volume and, thus, of pericardial constraint. Acute reduction of pericardial constraint has been

shown to increase CO in various animal models of pulmonary hypertension.^{5, 6} Finally (and speculatively), PTE may lead to improvement of RV coronary perfusion. Exorbitantly high RV pressure may increase intramyocardial pressure in the RV free wall and, thus, increase resistance of the RV coronary vasculature more than that of the LV. This may result in relatively reduced myocardial perfusion of the RV. The acute decrease of RV pressure with PTE may result in a decrease of RV coronary vascular resistance (facilitating RV myocardial perfusion) and also cause a decrease in RV mechanical myofiber load. Consequently, RV contractile function and stroke volume can improve.

Many studies have reported strong correlations between septal curvature and LV filling parameters such as E/A-ratio and speculated on the potential detrimental effect of leftward septal bulging on LV filling and RV performance in patients with pulmonary hypertension.^{22, 52, 59, 67, 72, 74, 86} The results of our study strongly support the concept that perturbations in LV filling pressure, output, and Doppler flow patterns due to CTEPH are primarily caused by diminished RV outflow and, hence, LV underfilling. Although not negligible, the relative contribution of septal geometry and bulging is considerably less. Also, the increases in cardiac output and LV filling explain the marked changes in LV Doppler diastolic filling pattern after PTE, rather than changes in septal geometry per se.

PATIENT-SPECIFIC MODELING TO ASSESS VENTRICULAR MECHANICAL ASYNCHRONY IN PULMONARY ARTERIAL HYPERTENSION

In PAH, the most distinct characteristic is the ventricular mechanical asynchrony as expressed by delay of peak shortening of the RV free wall and by early diastolic lengthening of the interventricular septum. In previous clinical studies, this ventricular mechanical asynchrony appeared related to disease severity and functional class of the patient.^{58, 69} Moreover, model simulations (**chapter 5**)⁶¹ as well as experimental data obtained in isolated hearts of rats with PAH37 show that early pacing of the RV free wall may decrease ventricular mechanical asynchrony and, thereby, improve RV pump function. Thus, ventricular mechanical asynchrony appears of significant diagnostic and therapeutic importance in patients with PAH. However, the precise mechanism by which PAH leads to ventricular mechanical asynchrony is poorly understood.

In **chapter 7**, a novel patient-specific fitting procedure is presented and applied to assess ventricular mechanics in a heterogeneous patient group consisting of PAH and CTEPH patients with and without right bundle branch

block (RBBB). Patient-specific simulations showed ventricular mechanical asynchrony in all patients. This asynchrony was evidenced by delay of peak shortening of the RV free wall and by early diastolic lengthening of the septum. Comparison of measured and simulated ventricular strain patterns revealed a systematic underestimation of early diastolic lengthening of the septum in the simulations. This underestimation suggests that the mechanical asynchrony can only partly be explained on the basis of physiological mechanical properties of the myocardial tissue. In a subgroup of patients with RBBB, agreement between measured and simulated ventricular mechanical asynchrony was further improved by additional delay of mechanical activation of the RV free wall. These findings suggest that, in PAH, ventricular mechanical asynchrony is caused by delay of mechanical relaxation of the RVfw. It has been shown that the asynchrony happened irrespective whether the delay of RVfw relaxation is caused by prolonged RVfw mechanical activation, delayed onset of RVfw activation, or both.

The suggested causality between delay of RVfw relaxation and ventricular mechanical asynchrony in PAH is supported by the findings of several clinical and experimental studies showing that chronic RV pressure overload is associated with significant electrophysiological remodeling in the myocardium of the RV free wall.^{18, 38, 53, 55} In patients with CTEPH, it has been shown that action potential duration is increased and conduction velocity is decreased in the RV free wall compared to those in the LV free wall.^{18, 38} Moreover, ventricular mechanical asynchrony appeared to be related to the time difference between LV and RV onset of electrical activation, the difference between LV and RV action potential duration, and the time difference between LV and RV repolarization. Several sarcolemmal ion currents are known to be significantly changed in the RV free wall of patients and experimental animals with chronic RV pressure overload.^{53, 55} The impact of electrophysiological remodeling as a result of RV pressure overload on global cardiac pump function in patients with PAH is hard to assess in vivo. In the future, more insight in the mechanism by which PAH leads to delay of mechanical myofiber relaxation in the RV free wall and, hence, ventricular mechanical asynchrony may be obtained by model simulations. For that purpose, the present model of sarcomere mechanics in the TriSeg model (**chapter 4, Appendix 4.B**) should be replaced by a more complex model describing subcellular electrophysiology and mechanoelectric feedback.^{48, 49}

In our patient-specific simulations based on normal physiological mechanical properties of the myocardial tissue (**chapter 7**), early diastolic septal lengthening was systematically underestimated. Interestingly, the degree of

underestimation correlated well with early diastolic septal lengthening as measured in the patients. It needs further investigation whether the amount of underestimation of early diastolic septal lengthening by our patient-specific simulation procedure is an indicator of myocardial pathology in the RV free wall. For that purpose, monitoring septal geometry and motion may be of considerable importance, since it has been shown that early diastolic lengthening of the septum corresponds to leftward septal bulging during LV isovolumic relaxation in our simulations of PAH (**chapters 4 and 5**) as well as in patients with severe PAH.^{32, 45, 64, 69, 90}

STUDY LIMITATIONS

In the TriSeg model, ventricular geometry is approximated by three thick-walled spherical segments encapsulating the LV and RV cavities (*Figure 4.2A*). In reality, LV geometry may be considered to be a thick-walled truncated ellipsoid. The relatively thin-walled RV free wall partially encapsulates the LV, giving the RV cavity a crescent shape when viewed in short-axis view (*Figure 2.5*). At the base, the ventricular cavities are enclosed by the non-contractile basal sheet with valves.⁸⁸ The simplification to spherical segments without a non-contractile sheet may have resulted in systematic errors of ventricular dimensions. Although there are indications of the importance of myocardial bending stiffness for simulation of septal geometry,^{8, 26} we neglected this effect for simplicity. Despite these inaccuracies, simulated ventricular hemodynamics as well as relative changes of ventricular dimensions during the cardiac cycle were surprisingly realistic. The fact that ventricular mechanics and hemodynamics are simulated so realistic is most likely a result of adaptation and of strict application of laws stating conservation of energy as applied to ventricular wall and cavity mechanics.

A crucial step in the TriSeg model is the calculation of myofiber strain from ventricular wall geometry in terms of midwall surface area and curvature (*Figure 4.3*). The one-fiber model by Arts *et al.*,¹ related myofiber strain to the ratio of cavity volume to wall volume. This model has previously been shown to be applicable to an anisotropic thick-walled structure like a myocardial wall when assuming rotational symmetry and homogeneity of mechanical load in the wall. In the TriSeg model, the relation between midwall area and myofiber strain was derived by applying the one-fiber model to a closed spherical cavity (**chapter 4, Eq. 4.15 and Appendix 4.A**). The resulting relation was then extended to a partial segment of the sphere by considering a fraction of the wall, having the same curvature, wall tension, and transmural pressure difference. The original

one-fiber model has been shown to be rather insensitive to wall geometry.¹ We expected the present relation between midwall area, curvature, and transmural pressure also to be quite insensitive to actual geometry. However, this fact has not been proven.

Animal studies have shown that the functional effect of asynchronous electrical activation is dramatic because the various regions differ not only in the time of onset of mechanical activation, but also in the pattern of contraction.⁷⁸ Early activated regions stretch not-yet activated remote regions. This stretching further delays shortening of the late-activated regions and increases their force of local contraction by virtue of the (local) Frank-Starling mechanism. Because of their vigorous contraction, the late-activated regions impose loading on the earlier activated territories, which may undergo systolic paradoxical stretch. This inhomogeneous pattern of contraction and stretching has been shown to cause a hemodynamically less effective and energetically less efficient ventricular contraction.⁴ This phenomenon is also observed in our simulations of cardiac mechanics with left bundle branch block (**chapter 3** and *Figure 3.6*) showing that mechanical myofiber work is significantly increased in the late-activated LV free wall and decreased in the earlier activated septum. These simulations indicate that mechanical ventricular interaction of the three ventricular walls is a very important mechanism for the hemodynamic changes associated with asynchronous mechanical activation of these walls. Due to its lumped character, the TriSeg model did not allow description of regional interactions within each wall segment but was limited to the description of its average representative myofiber mechanics. Especially with pacing of the dilated RV free wall of patients with severe PAH (**chapter 5**), the potential effect of heterogeneity of contractility and onset of activation within a single ventricular wall due to activation spread is not covered by the TriSeg model.

Although the TriSeg model can be easily modified to include a description of inhomogeneous myocardial wall properties, a finite element model of cardiac mechanics is more accurate and better suited to describe local inhomogeneities in mechanical load. For patient-specific modeling of the circulation, the model should simulate many cycles in order to find a best match with the available set of measurements. For that purpose, the TriSeg model is to be preferred because it allows almost real-time simulation of ventricular mechanics and hemodynamics, while calculation effort of a finite element model of both ventricles is more than 1,000 times larger.⁴⁴ The finite element model is absolutely needed to estimate and evaluate possible errors introduced by the applied simplifications of the TriSeg model.

In the present thesis, the external pressure surrounding the LV and RV free walls is assumed to be zero. The real heart is surrounded by the pericardium, which constrains increase of total heart volume during volume overload. Under normal resting conditions, the pericardium is believed to play a minor role, setting pericardial pressure close to zero.^{68, 73, 97} Also under chronic PAH conditions, the effect of the pericardium on ventricular mechanics is likely to be of minor importance, because measurements demonstrated adaptive dilatation of the pericardium in patients and experimental animals with chronic RV dilatation.^{10, 28} However, with acute increase of total heart volume, the pericardium affects cardiac hemodynamics and interaction of the cardiac chambers significantly.^{5, 15, 29} In our simulations of acute RV pressure overload in **chapter 4**, the effect of the pericardium should be considered because of severe RV dilatation (*Figure 4.5*) and increase of total heart volume. In our simulations of acute interventions in patients with PAH such as pacing (**chapter 5**) or pulmonary thromboendarterectomy (**chapter 6**), however, the effect of the pericardium is assumed to be negligible because these interventions lead to decrease of RV cavity volume.

An important limitation of our model is the fact that heart rate, ventricular stroke volume, and, hence, cardiac output are prescribed independent model parameters. In reality, however, these parameters are mutually dependent and are tightly controlled for maintenance of mean arterial blood pressure. As a result of structural adaptation, the ventricles of the normal heart are able to deliver the mechanical pump work needed to maintain normal arterial blood pressure under a wide range of loading conditions (exercise). In patients with severe PAH, exorbitant RV pressure overload increases mechanical myofiber load in the RV free wall above the level that can be compensated for by adaptation. Several studies showed that morbidity and mortality of PAH patients are determined by the ability of the RV to maintain normal stroke volume and cardiac output.^{19, 82} Unfortunately, the TriSeg model cannot be used to predict changes of cardiac output as a result of therapeutic interventions such as RV free wall pacing in severe PAH (**chapter 5**) or pulmonary thromboendarterectomy in CTEPH (**chapter 6**).

In our simulations of severely decompensated PAH (**chapter 5**), mechanical myofiber load was inhomogeneously distributed over the ventricular walls. In the RV free wall, myofiber stroke work was increased to almost three times normal values, whereas myofiber stroke work was decreased by about 20% in the LV free wall and the septum. When assuming stroke work density to be correlated to oxygen consumption,⁸⁹ the latter redistribution of myofiber stroke work implies a considerable increase of oxygen demand of the myocardium in

the RV free wall. Since oxygen supply is not included in our model, the potential effect of coronary perfusion imposed limitations on myocardial performance is unknown in our simulations of pulmonary hypertension.

With severe PAH, simulated ventricular mechanical asynchrony was systematically underestimated as compared to the asynchrony measured in patients (**chapters 5 and 7**). In our simulations of PAH, prolonged mechanical activation of the myofibers in the dilated RV free wall is explained by the normal physiological property of the cardiac muscle that duration of mechanical myofiber activation increases with sarcomere length. This latter property is well known from experiments on isolated cardiac muscle⁹³ and is as such implemented in the constitutive equations describing sarcomere mechanics in the TriSeg model (**chapter 4, Appendix 4.B**).⁶⁴ The systematic underestimation of ventricular mechanical asynchrony in the patient-specific simulations in **chapter 7** suggests that the abovementioned normal physiological behavior of the cardiac muscle is not sufficient to explain the ventricular mechanical asynchrony as measured in patients with severe PAH. Previous experimental studies showed that severe PAH is associated with structural and electrophysiological remodeling of the RVfw myocardium.^{12, 38} Ischemia^{33, 94, 100} and interstitial fibrosis^{9, 38, 60} in the RV free wall may locally change active and passive myocardial material properties in severe PAH. The disregarding of these pathophysiological aspects in the simulations of severe PAH may partially explain the discrepancy between simulated and measured ventricular mechanical asynchrony.

FUTURE PERSPECTIVES

The simulation results presented in **chapter 5** may provide a theoretical framework for a novel therapeutic strategy for severely decompensated PAH patients. Although decrease of pulmonary vascular resistance remains the primary therapeutic target in PAH patients, pacing of the RV free wall as an additional treatment may contribute to clinical improvement of the patient by unloading the myocardial tissue in the RV free wall and, thereby, delaying development of RV failure. Furthermore, it might be useful as bridge to thoracic organ transplantation in these patients. More experimental and clinical evidence is needed to prove that the predicted beneficial effect of RV free wall pacing is clinically relevant for a PAH patient.

Simulation results suggest that, in severe PAH, ventricular mechanical asynchrony is a direct consequence of increased myofiber stress in the RV free wall because of incomplete adaptation to increased load (**chapter 5**). Therefore,

it seems safe to assume that the ventricular mechanical asynchrony as measured in patients with severe PAH also indicates RV decompensation (**chapter 7**).⁶⁹ A spin-off of the present thesis may therefore be that ventricular mechanical asynchrony can be used as an index of RV decompensation.

Besides giving insight in the potential mechanism behind ventricular mechanical asynchrony in PAH patients, the study in **chapter 7** also presented a proof of principle showing that the model is feasible for patient-specific simulation of ventricular mechanics in a heterogeneous group of PAH patients. Especially in the subgroup of patients for which additional information about tricuspid regurgitation and right bundle branch block was used, realistic simulations of local ventricular strain patterns were obtained by fitting the model to a limited number of measured variables. Except for pulmonary artery pressure, all variables were measured non-invasively. Currently, the model is evaluated for its potential to patient-specifically simulate ventricular hemodynamics and mechanics in PAH patients using exclusively non-invasive measurements as input. For that purpose, non-invasive quantification of RV pressure is needed. In **chapter 4**, it has been shown that our model describes a linear relation between septal curvature and the pressure difference across the septum. This relation appeared similar to the one measured in a group of healthy adults and patients with PAH.^{21, 64, 79} Since it is relatively easy to image septal geometry non-invasively, we expect that it may be possible by patient-specific simulation to estimate RV pressure on the basis of exclusively non-invasive measurements. Such approach may pave the way for completely non-invasive patient-specific simulation of ventricular hemodynamics and mechanics in patients with PAH. Although we realize that invasive right heart catheterization will be necessary for clinical diagnosis of PAH, we think that a modeling approach may be useful for non-invasive patient-specific follow-up by monitoring the effect of therapeutic interventions. It may also enable a priori patient-specific quantification of the effect of therapeutic interventions such as pacing or thromboendarterectomy on cardiac pump function.

As shown in this thesis, the CircAdapt/TriSeg environment is versatile and flexible by its modular setup and enables realistic simulation of cardiovascular mechanics and hemodynamics under normal as well as various pathological conditions. Although the present thesis primarily focuses on PAH, previous trials^{43, 62, 63} showed that the model may also be a useful tool for *in silico* testing of hypotheses related to clinical and physiological issues in the field of cardiac resynchronization therapy.

GENERAL CONCLUSIONS

In this thesis, we gained more insight in the mechanisms by which pulmonary arterial hypertension (PAH) affects left ventricular (LV) and right ventricular (RV) pump function. We presented a novel mathematical model of cardiovascular mechanics incorporating hemodynamic and mechanical ventricular interaction. This model simulates ventricular mechanics and hemodynamics realistically under normal as well as pulmonary hypertensive ventricular loading conditions. With severe PAH, the model predicts similar ventricular mechanical asynchrony as measured in patients. Model simulations suggest that early pacing of the RV free wall in patients with severe PAH improves interventricular mechanical synchrony, decreases mechanical myofiber load in the RV free wall, and improves RV pump function. Furthermore, the model is used to assess the mechanism by which acute decrease of RV pressure overload by pulmonary thromboendarterectomy improves filling hemodynamics of the LV in patients with chronic thromboembolic pulmonary hypertension. These simulations show that increase of mitral E/A-ratio with pulmonary thromboendarterectomy is predominantly caused by increase of RV systolic output (hemodynamic ventricular interaction). The contribution of abolishment of leftward septal bulging due to decrease of RV pressure overload (mechanical ventricular interaction) is considerably less. Finally, a patient-specific simulation procedure is designed for assessment of ventricular mechanics and hemodynamics in the individual PAH patient. Patient-specific simulations are obtained by fitting the model to a limited set of measurements obtained in a heterogeneous group of PAH patients. Agreement between simulated and measured ventricular strain patterns shows that ventricular mechanical asynchrony can only partly be explained by normal physiological mechanical properties of the myocardial tissue. In a subgroup of PAH patients with right bundle branch block, agreement between simulated and measured ventricular mechanical asynchrony was further improved by introduction of an additional delay of mechanical activation of the RV free wall. These patient-specific simulations show that ventricular mechanical asynchrony is most likely caused by delay of mechanical relaxation of the RV free wall either due to prolonged mechanical activation of the RV free wall, delayed onset of mechanical activation, or both. The model presented in this thesis has been shown to be a valuable simulation tool for elucidating mechanisms of cardiac pathophysiology in PAH and for patient-specific assessment of ventricular mechanics and hemodynamics in patients with PAH.

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Summary

Pulmonary hypertension (PH) is characterized by elevated blood pressure in the pulmonary artery. The clinical classification of PH distinguishes five subgroups. Each subgroup shares pathological and clinical features as well as similar therapeutic options. In this thesis, we focus on pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), both resulting from elevated vascular resistance on the arterial side of the pulmonary circulation. PAH is characterized by progressive structural remodeling of the pulmonary arterioles. In CTEPH, pulmonary vascular resistance is elevated due to thrombi and resistive lesions in the more proximal pulmonary arteries. Unless stated differently, CTEPH is considered as a type of PAH in the remainder of this summary, since it also progressively develops due to similar histopathological changes in the pulmonary vasculature.

PAH is associated with chronic elevation of mechanical pump load of the right ventricle. When left untreated, PAH eventually leads to right heart failure and premature death. The underlying mechanisms by which PAH leads to heart failure are poorly understood. In this thesis, we elucidate the mechanisms by which PAH affects left ventricular (LV) and right ventricular (RV) pump function. These new insights are believed to be essential for improvement of therapy and diagnostics in patients with PAH. The general aim of this thesis as well as the specific aims of the separate studies, as included in this thesis, are briefly introduced in **chapter 1**.

In the human heart, the left ventricle (LV) and the right ventricle (RV) are functionally dependent due to mechanical ventricular interaction via the interventricular septum and due to hemodynamic ventricular interaction since RV outflow determines LV inflow. Consequently, PAH affects both ventricles as mentioned in **chapter 2**. A novel mathematical model of ventricular mechanics and hemodynamics (TriSeg model), incorporating ventricular interaction, has been developed and used for quantitative assessment of ventricular pump function under normal and PAH conditions.

In **chapters 3 and 4**, we present the theory behind the TriSeg model describing ventricular mechanics and hemodynamics incorporating mechanical interaction of the ventricular walls. Three wall segments representing the LV free wall, the interventricular septum, and the RV free wall are mechanically coupled, as expressed by the equilibrium of tensile forces in their junction. Global LV and RV pump mechanics are related to representative myofiber mechanics in the three ventricular walls, using prominently the principle of conservation of energy. Hemodynamic ventricular interaction is achieved by implementation of the TriSeg model in the modular CircAdapt model describing mechanics and

hemodynamics of the whole human circulation. The combined CircAdapt/TriSeg model allows realistic beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics such as volumes and pressures of the cardiac cavities, geometries and myofiber mechanics of the cardiac walls, and flows through the valves. Furthermore, the model allows adaptation of size and mass of cardiac walls and large blood vessels to normalize local mechanical load to tissue-specific physiological levels.

In **chapter 5**, severely decompensated PAH is simulated by increasing RV pressure load without adaptation. This simulation shows many similarities with data obtained in patients with severe PAH, e.g., RV dilatation, leftward septal bulging, and delayed peak shortening of the RV free wall as compared to that of the LV free wall and septum. Myofiber work in the RV free wall was three times higher than that in the septum and the LV free wall. In our model, we tested the hypothesis that RV resynchronization therapy improves ventricular mechanical synchrony and, thereby, RV pump function in PAH. Our model simulations show that preexcitation of the RV free wall relieves the RV free wall from the exorbitantly high myofiber work at the cost of an increase of myofiber work in the LV free wall and septum. Apparently, the mechanical interaction of the ventricular walls allowed redistribution of myofiber work over the ventricular walls. Upon 40-ms preexcitation of the RV free wall, mechanical load appeared most homogeneously distributed over the ventricular walls, RV and LV pressure curves were synchronized, and RV pump function was moderately improved. The latter improvement was evidenced by increase of RV $dP/dt_{\max}$, decrease of RV end-diastolic pressure, and decrease of RV end-diastolic volume. These simulations suggest that early pacing of the RV free wall is a potential treatment of RV failure in patients with severe PAH.

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), chronic increase of RV afterload is associated with an abnormal LV filling pattern, i.e., peak blood flow velocity of the early mitral filling wave (E-velocity) is smaller than that of the atrial contraction-induced late filling wave (A-velocity). Pulmonary thromboendarterectomy (PTE) is a surgical intervention that acutely reduces pulmonary vascular resistance and that is associated with acute increase of mitral E/A-ratio. Abolishment of leftward septal bulging and increase in RV systolic output are the two mechanisms that are thought to be responsible for the increase of the E/A-ratio with PTE. In **chapter 6**, the TriSeg model is used to estimate the separate contributions of both mechanisms in a group of CTEPH patients undergoing PTE. The effect of PTE on LV filling hemodynamics as predicted by our model is surprisingly similar to the effect as observed in

patients. Mitral E/A, mitral E-velocity, LV end-diastolic volume, and septal curvature increased from subnormal values in CTEPH before PTE to normal values after PTE, whereas RV end-diastolic volume decreased to normal value after PTE. Effects of RV pressure overload and of RV systolic output on LV filling hemodynamics are separated quantitatively by simulating either an exclusive decrease of mean pulmonary artery pressure or an exclusive increase of cardiac output, respectively. With exclusive decrease of mean pulmonary artery pressure, mitral E/A-ratio increased 26%, LV filling pressure decreased 16%, and leftward septal bulging was abolished. With exclusive increase of cardiac output, mitral E/A-ratio increased 53%, LV filling pressure increased 62%, whereas leftward septal bulging persisted. These data show that increase of mitral E/A-ratio with PTE in CTEPH patients is largely the effect of increased RV systolic output (hemodynamic ventricular interaction). Abolishment of leftward septal bulging (mechanical ventricular interaction) appears to be of less importance.

Finally, a novel patient-specific simulation procedure is presented in **chapter 7**. With this procedure, ventricular mechanics is assessed in a heterogeneous patient group consisting of PAH and CTEPH patients with and without right bundle branch block (RBBB). Patient-specific simulations showed ventricular mechanical asynchrony in all patients. This asynchrony was evidenced by delay of peak shortening of the RV free wall and by early diastolic lengthening of the septum. Comparison of measured and simulated ventricular strain patterns revealed a systematic underestimation of early diastolic lengthening of the septum in the simulations. Moreover, the underestimation was more pronounced in the simulations of patients with higher amplitude of early diastolic septal lengthening. This discrepancy between measurements and simulations may be explained by the fact that our sarcomere contraction model, as implemented in the TriSeg model, is based on experimental data obtained from isolated cardiac muscle under normal physiological loading conditions. In our PAH patients, however, the chronic increase of mechanical load of the RV myocardium likely modifies myocardial contraction. Nonetheless, most of our patient-specific simulations suggest that the ventricular mechanical asynchrony in PAH can largely be explained using regular mechanical properties of the myocardial tissue. In a subgroup of patients with RBBB, agreement between measured and simulated ventricular mechanical asynchrony was further improved when the onset of mechanical activation of the RV free wall was delayed, also resulting in delay of mechanical relaxation. These findings suggest that, in PAH, ventricular mechanical asynchrony is caused by delay of mechanical relaxation of the RV free wall. Furthermore, it has been shown that the asynchrony occurred irrespective whether the delay of

Summary

mechanical relaxation of the RV free wall was caused by prolonged mechanical activation of the RV free wall, delayed onset of activation, or both.

In conclusion, we presented a novel mathematical model of ventricular mechanics and hemodynamics, incorporating mechanical ventricular interaction. This model has been shown to be a valuable simulation tool for elucidating mechanisms of cardiac pathophysiology related to PAH and for patient-specific assessment of ventricular mechanics and hemodynamics in patients with PAH. Each of the studies presented in this thesis starts with fitting the model to the average of a set of clinical measurements obtained in patients with PAH in order to obtain a representative pathology-specific simulation. Using such pathology-specific simulation as point of departure, it is shown in our simulations that:

1. preexcitation of the RV free wall acutely improves RV pump function in PAH and, hence, RV pacing may be a potential treatment of RV failure in patients with severe PAH,
2. LV underfilling and not leftward septal bulging dominates abnormal LV filling hemodynamics in patients with CTEPH, and
3. ventricular mechanical asynchrony, as often present in PAH patients, is caused by delay of mechanical relaxation of the RV free wall compared to that of the LV free wall and the septum.

Samenvatting

Pulmonale hypertensie (PH) is de gemeenschappelijke naam voor een aantal aandoeningen die alle gekenmerkt worden door verhoogde bloeddruk in de longslagader (arteria pulmonalis). In de kliniek wordt op basis van pathologische, klinische en therapeutische criteria onderscheid gemaakt tussen vijf hoofdgroepen van PH. Het onderzoek in dit proefschrift richt zich op PH als gevolg van een verhoogde weerstand van de bloedvaten aan de slagaderlijke (arteriële) zijde van de longcirculatie. Dit is het geval bij pulmonale arteriële hypertensie (PAH) en chronische trombo-embolische pulmonale hypertensie (CTEPH). PAH wordt gekenmerkt door progressieve structurele remodelering van de pulmonale arteriolen. In het geval van CTEPH is de pulmonale vaatweerstand verhoogd als gevolg van trombi en vernauwende laesies in de proximale arteriën van de pulmonale circulatie. In het restant van deze samenvatting wordt CTEPH onder een noemer gebracht met PAH, tenzij anders vermeld.

De drukoverbelasting als gevolg van PAH leidt tot een verhoging van de pompbelasting van het rechter ventrikel van het hart. Zonder behandeling zal dit uiteindelijk leiden tot rechter hartfalen en vroegtijdige dood. De hedendaagse kennis van mechanismen die ten grondslag liggen aan hartfalen als gevolg van PAH is beperkt. Het onderzoek zoals beschreven in dit proefschrift, heeft als doel nieuw inzicht te verschaffen in de invloed van PAH op linker ventrikel (LV) en rechter ventrikel (RV) pompfunctie. Deze nieuwe inzichten zijn van essentieel belang voor verbetering van zowel therapie als diagnostiek in patiënten met PAH. In **hoofdstuk 1** zijn het algemene doel en de specifieke vraagstellingen van de afzonderlijke hoofdstukken van dit proefschrift kort uiteengezet.

In het menselijke hart zijn het linker en het rechter ventrikel functioneel afhankelijk van elkaar, enerzijds ten gevolge van mechanische interactie via het interventriculaire septum, anderzijds ten gevolge van hemodynamische interactie via de pulmonale en de systemische circulatie. In **Hoofdstuk 2** wordt beschreven hoe deze ventriculaire interactie ervoor zorgt dat PAH de pompfunctie van beide ventrikels beïnvloedt. Voor kwantitatieve beschrijving van ventriculaire pompfunctie zowel onder normale als onder PAH condities is een nieuw wiskundig model ontwikkeld (TriSeg model), dat de mechanica en hemodynamica van de ventrikels beschrijft inclusief de mechanische interactie tussen beide ventrikels. In **hoofdstukken 3 en 4** wordt de theorie beschreven die ten grondslag ligt aan het TriSeg model. In dit model worden de LV vrije wand, het interventriculaire septum en de RV vrije wand gerepresenteerd door drie afzonderlijke wandsegmenten die mechanisch gekoppeld zijn. Deze koppeling is wiskundig beschreven door een krachtenbalans. De relatie tussen de mechanica van globale ventriculaire pompfunctie en de mechanica van de

spiervezels in de wanden van de ventrikels wordt beschreven op basis van energiebehoud. Hemodynamische interactie tussen beide ventrikels is tot stand gebracht door integratie van het TriSeg model in het modulaire CircAdapt model, dat de mechanica en hemodynamica van het gehele menselijke cardiovasculaire systeem beschrijft. Het gecombineerde CircAdapt/TriSeg model maakt het mogelijk om de mechanica en de hemodynamica van de ventrikels realistisch en slag-op-slag te simuleren. Voorbeelden van beschikbare gesimuleerde grootheden zijn: ventriculaire holtevolumina en drukken, geometrie van de ventriculaire wanden, mechanica van de spiervezels in de ventriculaire wanden en stroming van bloed door de hartkleppen. Het model biedt de mogelijkheid tot simulatie van structurele adaptatie van het hart en de grote bloedvaten aan de mechanische belasting. Grootte en massa van hartspierwanden en bloedvaten worden aangepast zodat de lokale mechanische belasting van het weefsel in overeenstemming is met weefselspecifieke fysiologische normaalwaarden.

In **hoofdstuk 5** is ernstig gedecompenseerde PAH gesimuleerd door in het model de drukbelasting van het rechter ventrikel te verhogen zonder adaptatie toe te staan. De resulterende simulatie toont de volgende gelijkenissen met data die verkregen zijn in patiënten met ernstige PAH: RV dilatatie, linkswaartse buiging van het septum, relatieve vertraging van piekverkorting van de RV vrije wand ten opzichte van die van de LV vrije wand en het septum. In de simulatie is de spiervezelarbeid per hartslag drie keer groter in de RV vrije wand dan in de LV vrije wand en in het septum. Op basis van deze resultaten is de hypothese geformuleerd dat in patiënten met PAH vervroegde activatie van de RV vrije wand de ventriculaire mechanische synchronie herstelt en daardoor ook de RV pompfunctie verbetert. Onze simulaties tonen aan dat vervroegde activatie van de RV vrije wand in PAH zorgt voor een verlaging van de buitensporig hoge spiervezelarbeid in de RV vrije wand en voor een verhoging van de arbeid die verricht wordt door de spiervezels in de LV vrije wand en in het septum. Deze redistributie van spiervezelarbeid wordt mogelijk gemaakt door de mechanische koppeling van de ventriculaire wanden. Wanneer de RV vrije wand 40 ms eerder geactiveerd wordt dan de LV vrije wand en het septum, is de mechanische belasting het meest homogeen verdeeld over de ventriculaire wanden, zijn de RV en de LV drukcurven synchroon en is de RV pompfunctie verbeterd. Deze laatste verbetering komt tot uiting door een toename van $RV\ dP/dt_{max}$, door afname van RV eind-diastolische druk en door afname van RV eind-diastolisch volume. Onze simulaties suggereren dat vervroegde activatie van de RV vrije wand mogelijk gebruikt kan worden voor behandeling van rechter hartfalen in patiënten met ernstige PAH.

In patiënten met chronische trombo-embolische pulmonale hypertensie (CTEPH) gaat de chronische verhoging van RV afterload gepaard met een abnormaal LV vullingpatroon: piek bloedstroomsnelheid door de mitralisklep tijdens de vroege passieve vullingfase (E-snelheid) is kleiner dan die tijdens de late actieve vullingfase (A-snelheid). Deze actieve vullingfase wordt geïnduceerd door contractie van het linker atrium. CTEPH patiënten kunnen behandeld worden met pulmonale trombo-endarteriëctomie (PTE). Tijdens deze ingreep worden trombi en vernauwende laesies in het pulmonale vaatbed waar mogelijk chirurgisch verwijderd. PTE resulteert in de meeste gevallen in een acute reductie van de pulmonale vaatweerstand (en dus ook van RV druk) en een acute verhoging van de mitralis E/A-ratio (E/A). De daling van RV druk als gevolg van PTE zorgt voor een verandering van de beweging van het septum, namelijk van abnormale linkswaartse buiging voor PTE naar normale rechtswaartse buiging na PTE. De stijging van E/A met PTE kan verklaard worden aan de hand van twee mechanismen, namelijk opheffing van het naar links doorbuigen van het septum en toename van RV systolische output. Het TriSeg model is in **hoofdstuk 6** gebruikt om de afzonderlijke bijdragen van beide mechanismen te kwantificeren in een groep patiënten met CTEPH die PTE ondergaan. Het effect van PTE op LV vulling hemodynamica zoals het door ons model wordt voorspeld, is kwantitatief in overeenstemming met het effect zoals gemeten in patiënten. Zo voorspelt ons model dat E/A, E-snelheid en LV eind-diastolisch volume stijgen van subnormale waarden in CTEPH naar normale waarden na PTE. Bovendien normaliseert de kromming van het septum (van linkswaarts naar rechtswaarts) en daalt RV eind-diastolisch volume naar een normale waarde na simulatie van PTE. De afzonderlijke effecten van RV drukbelasting en van RV systolische output op de vulling hemodynamica van de LV zijn met behulp van het model kwantitatief gescheiden door respectievelijk alleen een afname van gemiddelde bloeddruk in de arteria pulmonalis ofwel alleen een toename van cardiac output te simuleren. Met enkel afname van de gemiddelde druk in de arteria pulmonalis neemt E/A 26% toe, neemt LV vullingdruk met 16% af en verdwijnt de linkswaartse buiging van het septum. Met enkel toename van cardiac output nemen E/A en LV vullingdruk met respectievelijk 53% en 62% toe, terwijl de linkswaartse buiging van het septum persisteert. Deze data suggereren dat de toename van E/A na behandeling met PTE van patiënten met CTEPH voornamelijk het gevolg is van toename van RV systolische output (hemodynamische ventriculaire interactie). Opheffing van de linkswaartse buiging van het septum (mechanische ventriculaire interactie) lijkt een minder belangrijke rol te spelen in de normalisatie van het LV vullingpatroon.

Tenslotte is in **hoofdstuk 7** de ontwikkeling van een nieuwe patiënt-specifieke simulatiemethode beschreven. Deze methode is gebruikt voor kwantitatieve benadering van ventriculaire mechanica in een studiegroep bestaande uit patiënten met pulmonale hypertensie van verschillende etiologie (PAH of CTEPH) met of zonder rechter bundeltakblok (RBTB). De patiënt-specifieke simulaties vertonen ventriculaire mechanische asynchronie in alle patiënten. Deze asynchronie wordt gekenmerkt door vertraging van piek verkorting van de RV vrije wand en door vroegtijdige verlenging van het septum aan het begin van LV diastole. Een vergelijking van gesimuleerde met gemeten ventriculaire strainpatronen heeft onthuld dat het model de vroegtijdige diastolische verlenging van het septum systematisch onderschat. Bovendien bleek deze onderschatting relatief groter te zijn in simulaties van patiënten met een grotere amplitude van vroegtijdige diastolische verlenging van het septum. Een mogelijke verklaring voor deze discrepantie tussen meting en simulatie kan liggen in het feit dat het contractie-model van de sarcomeer in het TriSeg model gebaseerd is op experimentele data die verkregen zijn in geïsoleerde hartspiercellen onder fysiologische mechanische belasting. Echter, in PAH-patiënten is de mechanische belasting van het RV hartspierweefsel zeer waarschijnlijk chronisch verhoogd en gelden mogelijk andere contractiemodellen. Desalniettemin wekken onze patiënt-specifieke simulaties sterk de indruk dat de ventriculaire mechanische asynchronie in PAH gedeeltelijk verklaard kan worden aan de hand van fysiologische mechanische eigenschappen van het hartspierweefsel. Door de start van mechanische activatie (en dus ook de relaxatie) van de RV vrije wand te vertragen is in een subgroep van patiënten met RBTB de gesimuleerde ventriculaire mechanische asynchronie in kwantitatieve overeenstemming gebracht met de gemeten asynchronie. Deze bevinding suggereert dat de ventriculaire mechanische asynchronie in PAH veroorzaakt wordt door vertraging van mechanische relaxatie van de RV vrije wand ten opzicht van die van de LV vrije wand en het septum. Onze simulaties tonen ook aan dat asynchronie optreedt ongeacht de exacte oorzaak van de vertraging van de mechanische relaxatie van de RV vrije wand. Zowel een verlengde duur van mechanische activatie als een vertraagde start van activatie of zelfs beide effecten tegelijkertijd kunnen de mechanische asynchronie veroorzaken.

Samenvattend is in dit proefschrift een nieuw wiskundig model gepresenteerd, dat de mechanica en hemodynamica van de ventrikels beschrijft inclusief de mechanische interactie tussen de ventriculaire wanden. Verder hebben we laten zien dat het model enerzijds nuttig kan zijn voor fundamenteel onderzoek naar mechanismen van cardiale pathofysiologie in PAH en anderzijds voor patiënt-specifieke benadering van ventriculaire mechanica en hemodynamica in patiënten

met PAH. Elke afzonderlijke studie van dit proefschrift begint met het in overeenstemming brengen van het model met de gemiddelde waarden van een set klinische metingen verkregen in patiënten met PAH. Op die manier wordt voor elke studiegroep een representatieve pathologie-specifieke simulatie verkregen. Startende vanuit een dergelijke pathologie-specifieke simulatie is aan de hand van simulaties aangetoond dat:

1. vervroegde activatie van de RV vrije wand resulteert in een acute verbetering van RV pompfunctie in PAH en dus mogelijk gebruikt kan worden voor behandeling van rechter hartfalen in patiënten met ernstige PAH;
2. vooral LV ondervulling en in mindere mate de linkswaartse buiging van het septum zorgt voor een abnormaal LV vullingpatroon in patiënten met CTEPH; en
3. ventriculaire mechanische asynchronie in PAH veroorzaakt wordt door vertraging van mechanische relaxatie van de RV vrije wand ten opzichte van die van de LV vrije wand en het septum.

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Dit proefschrift is tot stand gekomen mede door de inspanning en kennis van vele anderen. Daarom zou ik graag willen besluiten met een woord van dank gericht tot iedereen die een bijdrage heeft geleverd, in welke vorm dan ook. Een aantal mensen wil ik in het bijzonder bedanken.

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Curriculum Vitae

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was born on May 28, 1982, in Sittard, The Netherlands.

From 1994 until 2000, he attended secondary education at Trevianum in Sittard where he obtained his Gymnasium (β) diploma. In 2000, he started his academic education at Eindhoven University of Technology where he obtained his Bachelor of Science degree (BSc) in Biomedical Engineering in September 2003 and his Master of Science degree (MSc) in Medical Engineering with the designation 'With Great Appreciation' in November 2005. During the Master Program, he did an internship at the Bioengineering Institute of the University of Auckland in New Zealand (January - April 2005) under the supervision of Assoc. Prof. Alistair A. Young. Furthermore, he did his final Master project, entitled "Effect of Aging on Left Ventricular Mechanics", at the Department of Biophysics at the Cardiovascular Research Institute Maastricht (CARIM) of Maastricht University under the supervision of Prof. Theo Arts and Dr. Tammo Delhaas. From 2006 until 2010, he worked as a PhD candidate at the Departments of Physiology and Biophysics (currently Department of Biomedical Engineering) at Maastricht University, again under the supervision of Prof. Theo Arts and Dr. Tammo Delhaas. During this PhD project, he used a patient-specific modeling approach to study the mechanisms of right heart failure in patients with pulmonary arterial hypertension. As of March 2010, he is working as a Postdoctoral Research Fellow at the Department of Biomedical Engineering at Maastricht University.

List of Publications

The background is a dark charcoal gray. It features two large, overlapping heart shapes in a slightly lighter shade of gray. Overlaid on these hearts are two sets of concentric circles, also in a medium gray tone. One set of circles is positioned on the left heart, and the other is on the right heart. The circles are of varying diameters, creating a layered, geometric effect.

PEER-REVIEWED JOURNAL ARTICLES

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BOOK CHAPTERS

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Juf

"Wat wil je worden" vroeg de juf,
't was in de derde klas,
ik keek haar aan en wist het niet,
'k dacht dat ik al iets was.

Toon Hermans